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14. ABSTRACT

Development of novel technologies and therapeutic agents to treat Duchenne muscular dystrophy (DMD) have increased interest by regulatory bodies such as the Food and Drug Administration in the development of "clinically-meaningful" study endpoints for clinical trials. There is a need for the development of person-reported outcome (PRO) instruments that target a broad range of developmental and functional ability while effectively evaluating treatment effects in clinical trials.

Our proposed project will use quality of life questionnaire data from the first 4-7 years of ongoing Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study. Using that data, we will identify questions that show differences between people with different levels of abilities (such as those who can walk or just raise a hand to the mouth), or that show changes over one year that might be seen by researchers during drug clinical trials. Those questions will then be combined and built into a computerized adaptive testing (CAT) system that will produce short, individualized surveys for clinical practice and clinical trial use that are tailored to a patients' level of functional ability.

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TABLE OF CONTENTS

1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

Background: Development of novel technologies and therapeutic agents to treat Duchenne muscular dystrophy (DMD) have increased interest by regulatory bodies such as the Food and Drug Administration in the development of "clinically-meaningful" study endpoints for clinical trials. There is a need for the development of person-reported outcome (PRO) instruments that target a broad range of developmental and functional ability while effectively evaluating treatment effects in clinical trials.
Objective: Our proposed project will use quality of life questionnaire data from the first 4-7 years of ongoing Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study. Using that data, we will identify questions that show differences between people with different levels of abilities (such as those who can walk or just raise a hand to the mouth), or that show changes over one year that might be seen by researchers during drug clinical trials. Those questions will then be combined and built into a computerized adaptive testing (CAT) system that will produce short, individualized surveys for clinical practice and clinical trial use that are tailored to a patients' level of functional ability.
Applicability: Well-designed CAT-PRO questionnaires can be used in both clinical trials and day-to-day clinical practice. For clinical trials, they provide researchers with the ability to put all patients, regardless of their functional abilities, together on the same scale. That means that one tool can be used to evaluate quality of life across many types of studies and many groups of patients, but that the results can still be compared. Those results can then also be compared to other clinical trial measures such as strength tests, timed function tests, or pulmonary function tests to help teach researchers and regulatory authorities about how "in clinic" tests commonly used in clinical trials relate to a persons' quality of life, and whether those tests are "clinically meaningful". In day-to-day clinical practice, it means that doctors can have a single tool that can give feedback on a patient's quality of life, even as their levels of ability change over time. Within 3 years, this project will be able to produce such a useful tool because much of the data has already been collected from the CINRG study and because the rest of the data will be from the large group of over 3000 volunteers who are already part of the Parent Project Muscular Dystrophy DuchenneConnect Registry.
Impact and Contributions: Data from the CINRG DMD natural history study cohort and the DuchenneConnect Registry will provide the basis for development of a "clinical trial-ready" novel CAT-based PRO measure that has been constructed against a background of comprehensive clinical assessments of strength and function across the DMD lifespan. This PRO measure will be rapidly usable as a sensitive measure for use in the growing field of DMD clinical trials, and will help to demonstrate "clinically meaningful" results to regulatory agencies in charge of new drug approval.

2. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

Duchenne muscular dystrophy
Person-reported outcomes
Health-related quality of life
Functional health assessment
UC Davis / CINRG Duchenne Natural History Study

3. **ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.

What were the major goals of the project?

Administrative Note: In the second year of this project we experienced significant programmatic delays within our research group, in part due to the departure of key staff member Data Manager Mr. de Bie who has now been replaced by Data Manager Corey Owens. In addition, delays occurred due to the movement of the CINRG Coordinating Center and the CINRG Duchenne Natural History Study (DNHS) from Children's National Medical Center to Therapeutic Research in Neuromuscular Disorders Solutions *(*TRiNDS*)*. Staffing issues have been resolved, the DNHS study is currently re-starting, and we are presenting a revised study timeline reflecting an additional no-cost extension year, which will be formally requested in parallel with this progress report. We feel that our new timeline reflects a schedule that will enable us to adequately complete the proposed aims without major modifications. Revised timelines are noted in the discussion below for each Specific Aim and Task, and will occur according to the following schedule:

Original Timeline

	Y1				Y2				Y3			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Aim 1.1												
Task 1	X											
Task 2	X											
Task 3	X											
Aim 1.2												
Task 1		X										
Aim 1.3												
Task 1	X	X										
Task 2			X									
Task 3			X									
Task 4			X									
Aim 2												
Task 1			X									
Task 2			X									
Task 3			X									
Task 4			X	X	X	X	X	X				
Aim 2.1												
Task 1								X				
Aim 2.2												
Task 1								X				
Aim 3												
Aim 3.1												
Task 1									X	X	X	X
Aim 3.2												
Task 1									X	X	X	X
Task 2									X	X	X	X
Task 3									X	X	X	X

Revised Timeline

	Y1				Y2				Y3				Y4			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Aim 1.1																
Task 1	X															
Task 2	X															
Task 3	X															
Aim 1.2																
Task 1		X														
Aim 1.3																
Task 1									X							
Task 2			X													
Task 3									X	X	X					
Task 4			X	X	X	X	X	X	X	X	X					
Aim 2																
Task 1			X					X	X	X						
Task 2			X								X					
Task 3											X					
Task 4			X	X	X	X	X	X			X	X	X	X	X	
Aim 2.1																
Task 1								X							X	
Aim 2.2																
Task 1								X							X	X
Aim 3																
Aim 3.1																
Task 1									X	X	X	X	X	X	X	X
Aim 3.2																
Task 1									X	X	X	X		X		
Task 2									X	X	X	X		X		
Task 3									X	X	X	X			X	X

Aim 1: Development of ICF-based Item Banks from CINRG DNHS PRO Data (Year 1, Months 1-6) - We will evaluate item responses across domains to develop domain-specific item banks for a composite PRO measure. We will evaluate responsiveness of PRO subscales and items at differing levels of function that represent functionally-meaningful activities of standing from supine, climbing stairs, rising from a chair, ambulating independently, reaching overhead, raising a hand to the mouth for feeding, and the need for mechanical cough assistance for airway clearance (defined as having a forced vital capacity >50% of predicted values for age). Data will include all available completed PRO form sets for all participants from the baseline visit up to at least the month 48 visit, and will an age range of 5-32+ years, which will represent approximately 1200+ 12-month intervals. Clinical data will include steroid treatment status, anthropometrics, timed motor performance testing (time to stand from supine, time to climb 4 stairs, time to run/walk 10 meters), Brooke and Vignos scales, and forced vital capacity pulmonary function. Some data from the cohort will be available out to 7 years of participation. At each visit time point, participants will be classified into a functional milestone group as previously described. Using that milestone grouping, we will evaluate 12-month change for each year of study participation. Those who increase in milestone scale score will be classified as having lost a functional milestone during that period. Participants will also be classified by steroid-user status as glucocorticoid naïve, previously-treated or currently-treated. Their questionnaire responses will be scored into instrument total and subscale scores per standard guidelines. Responses on all individual items will also be evaluated independently. Each instrument subscale and item will be classified according to ICF domain and subdomain for inclusion in domain-based item banks. Level of significance will be set at $p<0.05$.

Aim 1.1: Selection of Initial Item Bank Content (Year 1, Month 1-3) – Using all available PRO data, we will evaluate item responses across domains to develop domain-specific item banks for a composite PRO measure. We will evaluate responsiveness of PRO subscales and items at differing levels of function that represent functionally-meaningful activities of standing from supine, climbing stairs, rising from a chair, ambulating independently, reaching overhead, raising a hand to the mouth for feeding, and the need for mechanical cough assistance for airway clearance (defined as having a forced vital capacity >50% of predicted values for age).

- Task 1 (COMPLETE) – Human Subject Protection Approval Submission to DoD (Weeks 1-2): In collaboration with data management staff at the Cooperative International Neuromuscular Research Group, we will submit IRB approvals from sites engaged in the CINRG Duchenne Natural History Study (DNHS). The project is currently funded by DoD and site approvals have been obtained previously. As this portion of the project involves data analysis only, no additional research aims require addition to the original study protocol. Participants have already consented to collection and analysis of PRO data by the project PI and CINRG collaborators. DoD-specific consent language has been added as required and consent for project participation has been collected from participants. This subtask will be conducted by Dr. Henricson and Mr. de Bie.
- Task 2 (COMPLETE) - Dataset curation and formatting (Weeks 3-4): In collaboration with data management staff at the Cooperative International Neuromuscular Research Group, we will reference the full-scale dataset from the CINRG Duchenne Natural History Study (DNHS) to construct an analysis-ready dataset including the functional milestone and PRO item responses required in the Aim 1 analysis. This subtask will be conducted by Dr. Henricson and Mr. de Bie.
- Task 3 (COMPLETE) - PRO data analysis and WHO-ICF domain-based item bank construction (Week 4-Month 3): PRO instrument items will be evaluated to construct item banks based on the WHO-ICF domain structure. This subtask will be conducted by Dr. Henricson.

Aim 1.2 (Year 1, Month 4-5): To refine the item banks and ensure coverage across the entire spectrum of disease, we will identify ranges of function where overlapping PRO items or gaps in item content exist against a

backdrop of the entire range of meaningful functional abilities demonstrated by the DMD population across all age groups.

- Task 1 (COMPLETE) – Factor analysis and Rasch analysis to identify item bank performance (Months 4-5). Analysis for this aim will be conducted by Dr. Bagley, with the input and assistance of Dr. Henricson, Dr. McDonald and Dr. Joyce.

Aim 1.3: Focus Groups to Develop Supplemental Domain Items *(Revised to Year 1 Month 9 - Year 3)* – To address areas of overlap and gaps in item content, we will conduct focus group discussions with an expert advisory group of DMD clinical research professionals, health care providers, parent caregivers, and patients with DMD to identify relevant items for inclusion in a composite PRO measure, and to develop new items where suitable ones do not exist.

- Task 1 (COMPLETE) – Human Subject Protection Approval Submission to DoD (Months 1-6): The project PI and co-investigators will develop a human subjects protocol and consent documentation for key informant interviews and focus groups, and will obtain IRB approval from UC Davis. UC Davis IRB approvals will be submitted to DoD HRPO for revision and approval. DoD revisions will be reviewed and approved by the UC Davis IRB. This task will be completed by Dr. McDonald, Dr. Henricson, Dr. Joyce and Mr. Owens.
- Task 2 (COMPLETE) – Clinical expert key informant interviews (Month 6): Areas of overlap and gaps in item content will be discussed via teleconference with a group of DMD clinical experts to identify possible question content to supplement the existing item banks. This task will be conducted by Dr. Joyce and Dr. Henricson with the assistance of outreach coordinator Erica Goude.
- Task 3 (IN PROGRESS) – Patient and Caregiver focus groups *(Revised to Year 3 Months 1-9)*: Areas of overlap and gaps in item content will be discussed in small focus groups of DMD patients and parents/guardians in face-to-face meetings at the UC Davis Center for Neuromuscular Disease Research. This task will be conducted by Dr. Joyce and Dr. Henricson with the assistance of outreach coordinator Erica Goude.
- Task 4 (IN PROGRESS) – Existing PRO item review and new item generation *(Revised to Month 6 - Year 3 Month 9)*: The frequently mentioned and most relevant items will be compared to existing PRO tools to determine whether there are pre-existing question items that can be included in the item banks. Where none exist, new items will be developed and reviewed with focus group participants from Task 2 prior to inclusion. This task will be conducted by Dr. Joyce, Dr. McDonald, Dr. Mulcahey and Dr. Henricson.

AIM 2: Pilot Testing of WHO-ICF Domain Item Banks using DuchenneConnect *(Revised to Year 2 Month 9 – Year 4 Month 9)* – DuchenneConnect is a web-based DMD patient data registry and epidemiology research tool hosted by Parent Project Muscular Dystrophy that is used by more than 3000 families worldwide to track important clinical data related to the health, function and health services utilization of their family member(s) with DMD. We will work with DuchenneConnect administrators to publish an online version of the full PRO banks including all final items across domains. We will ask DuchenneConnect participants to enroll in the study and complete question sets at baseline. One year later participants will be contacted by email and reminded to complete a follow-up set of assessments after 1 year of follow-up. Data will be combined with registry self-report glucocorticoid use and measures of functional "milestone" ability data.

- Task 1 (90% COMPLETE) – Development of web-based item bank questionnaires *(Revised to Year 2 Month 12 – Year 3 Month 6)*: Using final pilot item banks developed in Aim 1, Dr. Henricson and Mr.

Owens will work with PPMD DuchenneConnect representatives to construct a web-based version of item bank questionnaires and the related back-end database and accompanying data dictionary.

- Task 2 – IRB review and approval of web-based DuchenneConnect item bank questionnaires *(Revised to Year 3 Month 8)*: Dr. Henricson and Mr. Owens will coordinate IRB submission and review of web-based questionnaires and recruiting materials. This is a minimal risk study and can be processed at UC Davis via expedited IRB review.
- Task 3 – Human Subject Protection Approval Submission to DoD *(Revised to Year 3 Month 8)*: UC Davis IRB approvals will be submitted to DoD HRPO for revision and approval. DoD revisions will be reviewed and approved by the UC Davis IRB. This task will be completed by Dr. McDonald, Dr. Henricson, and Mr. Owens
- Task 4 – Recruiting and launch of web-based forms in collaboration with DuchenneConnect *(Revised to Year 3 Month 9 – Year 4 Month 9)*: UC Davis outreach coordinator Erica Goude will collaborate with DuchenneConnect staff to provide email outreach and study recruiting to all participating DuchenneConnect members. This activity will continue until the end of Year 2.

Aim 2.1: Validation of New Domain-Based Item Banks *(Revised to Year 4 Month 4 – Year 4 Month 9)* – Prospective 1-year data from the DuchenneConnect registry application of newly-derived item banks will be evaluated using techniques described in Aim 1 to confirm that items are responsive to self-reported changes in milestone ability over a time period consistent with design of contemporary clinical trials. Rasch analysis will be repeated to confirm item fit and performance for retained and newly-developed items.

- Task 1 – Confirmatory Rasch Analysis *(Revised to Year 4 Month 7)*: Item response data collected via DuchenneConnect will be tested to confirm responsiveness to changes in self-reported functional milestone abilities. Item responses for the draft item banks including new items directed to fill "gaps" will be re-analyzed by RASCH to confirm their item fit and performance. Dr. Bagley will conduct this activity, with input and data review by Dr. McDonald, Dr. Mulcahey, Dr. Joyce, and Dr. Henricson

Aim 2.2: Identification of Item Responsiveness to Group Differences Due to Glucocorticoid Therapy *(Revised to Year 4 Month 7)* – Evaluate the responsiveness of the composite PRO item banks to differences in milestone scores. We will test the hypothesis that functionally-specific mobility and ADL PRO items will be differentially responsive functional "milestone" abilities.

- Task 1 – Evaluation of responsiveness to differences functional "milestone" ability *(Revised to Year 4 Month 7)*. Dr. Bagley and Dr. Henricson will conduct this activity, with input and data review by Dr. McDonald, Dr. Mulcahey, and Dr. Joyce.

AIM 3: Development of a Computerized Adaptive Testing PRO instrument for use in clinical trials *(Revised to Year 4 Month 7 – Year 4 Month 12)*:
In the third year of the project, we will use Year 2 pilot data to develop a brief computerized adaptive testing (CAT) version of the new composite PRO instrument, and we will make it available to the clinical research community for inclusion in natural history studies and clinical trials for persons with DMD.

Aim 3.1: Perform a CAT simulation from data obtained from the comprehensive PRO item banks (Revised to Year 4). A real data simulation approach will be used to investigate the accuracy of each CAT generated from the full-item banks.

- Task 1: Dr. Mulcahey will lead the group in developing CAT simulations for 5-, 10- and 15-item computer adaptive tests.

Aim 3.2: Establish discriminant and concurrent validity of the CAT version of the composite PRO in parents/ caregivers of DMD subjects (Revised to Year 4 Month 6 – Year 4 Month 12). Evaluation of the ability of the mobility and daily routines full-item banks and the 5-, 10-, and 15-item simulated CATs to discriminate between and among groups of DMD subjects.

- Task 1 – IRB review and approval of CAT PRO simulations *(Revised to Year 4 Month 6)*: Dr. Henricson and Mr. Owens will coordinate IRB submission and review of CAT simulation protocols and recruiting materials to enbroll 80 DNHS participants at UC Davis. This is a minimal risk study and can be processed at UC Davis via expedited IRB review.
- Task 2 – Human Subject Protection Approval Submission to DoD *(Revised to Year 4 Month 6)*: UC Davis IRB approvals will be submitted to DoD HRPO for revision and approval. DoD revisions will be reviewed and approved by the UC Davis IRB. This task will be completed by Dr. McDonald, Dr. Henricson, and Mr. Owens
- Task 3 – *(Revised to Year 4 Month 7 – Year 4 Month 12)*: Dr. Mulcahey will lead the group in comparing results of newly-developed CAT evaluations to functional performance data collected on 80 DNHS participants enrolled at UC Davis in conjunction with their regularly scheduled study visits.

What was accomplished under these goals?

Aim 1: Development of ICF-based Item Banks from CINRG DNHS PRO Data (Year 1, Months 1-6) - We will evaluate item responses across domains to develop domain-specific item banks for a composite PRO measure. We will evaluate responsiveness of PRO subscales and items at differing levels of function that represent functionally-meaningful activities of standing from supine, climbing stairs, rising from a chair, ambulating independently, reaching overhead, raising a hand to the mouth for feeding, and the need for mechanical cough assistance for airway clearance (defined as having a forced vital capacity >50% of predicted values for age). Data will include all available completed PRO form sets for all participants from the baseline visit up to at least the month 48 visit, and will an age range of 5-32+ years, which will represent approximately 1200+ 12-month intervals. Clinical data will include steroid treatment status, anthropometrics, timed motor performance testing (time to stand from supine, time to climb 4 stairs, time to run/walk 10 meters), Brooke and Vignos scales, and forced vital capacity pulmonary function. Some data from the cohort will be available out to 7 years of participation. At each visit time point, participants will be classified into a functional milestone group as previously described. Using that milestone grouping, we will evaluate 12-month change for each year of study participation. Those who increase in milestone scale score will be classified as having lost a functional milestone during that period. Participants will also be classified by steroid-user status as glucocorticoid naïve, previously-treated or currently-treated. Their questionnaire responses will be scored into instrument total and subscale scores per standard guidelines. Responses on all individual items will also be evaluated independently. Each instrument subscale and item will be classified according to ICF domain and subdomain for inclusion in domain-based item banks. Level of significance will be set at $p<0.05$.

Aim 1.1: Selection of Initial Item Bank Content (Year 1, Month 1-3) – Using all available PRO data, we will evaluate item responses across domains to develop domain-specific item banks for a composite PRO measure. We will evaluate responsiveness of PRO subscales and items at differing levels of function that represent functionally-meaningful activities of standing from supine, climbing stairs, rising from a chair, ambulating independently, reaching overhead, raising a hand to the mouth for feeding, and the need for mechanical cough assistance for airway clearance (defined as having a forced vital capacity >50% of predicted values for age).

- *Accomplishments and Results:* Results of our item responsiveness analysis are presented in detail in *Appendix 1: Initial Developlment of the Duchenne Muscular Dystrophy Lifetime Mobility Scale by Rasch Analysis* beginning with the *Results* section on Page 5 of 35 and continuing through the *Principle Components Analysis* section on Page 8 of 35.

Aim 1.2 (Year 1, Month 4-5): To refine the item banks and ensure coverage across the entire spectrum of disease, we will identify ranges of function where overlapping PRO items or gaps in item content exist against a backdrop of the entire range of meaningful functional abilities demonstrated by the DMD population across all age groups.

- *Accomplishments and Results:* Results of our initial item bank evaluation are presented in Appendix 1 beginning on Page 8 of 35 under the *First-Pass Rasch Analysis* section and continuing to the top of Page 12 of 35. Selection of final model domains and refinement of those item banks for those domains via a second pass Rasch analysis is presented beginning on Page 12 of 35 and continuing through the *Revisions to Question Syntax and Response Structure* section which begins at the top of Page 23 of 35.

Aim 1.3: Focus Groups to Develop Supplemental Domain Items *(Revised to Year 1 Month 9 - Year 3)* – To address areas of overlap and gaps in item content, we will conduct focus group discussions with an expert advisory group of DMD clinical research professionals, health care providers, parent caregivers, and patients with DMD to identify relevant items for inclusion in a composite PRO measure, and to develop new items where suitable ones do not exist.

- *Accomplishments and Results:* Input from the expert advisory group is described in the previously referred to section of Appendix 1 entitled *Grouping Question Items by WHO-ICF Domains* on Page 5 of 35 and the *Principle Components Analysis* section on Page 8 of 35. Additional input from our expert advisors resulted in the inclusion of question items reflecting tasks from various commonly-used clinical evaluations. These additional items are discussed in the section entitled *Comparable instruments from clinical practice; The North Star Ambulatory Assessment, Egen Klassifikation Scale and Performance of the Upper Limb (PUL) Assessment* beginning on Page 24 of 35. Data collection efforts for parent / caregiver and patient feedback using the expanded question set including those identified through expert review are currently underway and protocol details are attached in human subject study protocol form as Appendix 2. Data collection and evaluation are anticipated to be complete by the mid-August, 2017.

AIM 2: Pilot Testing of WHO-ICF Domain Item Banks using DuchenneConnect *(Revised to Year 2 Month 9 – Year 4 Month 9)* – DuchenneConnect is a web-based DMD patient data registry and epidemiology research tool hosted by Parent Project Muscular Dystrophy that is used by more than 3000 families worldwide to track important clinical data related to the health, function and health services utilization of their family member(s) with DMD. We will work with DuchenneConnect administrators to publish an online version of the full PRO banks including all final items across domains. We will ask DuchenneConnect participants to enroll in the study and complete question sets at baseline. One year later participants will be contacted by email and reminded to complete a follow-up set of assessments after 1 year of follow-up. Data will be combined with registry self-report glucocorticoid use and measures of functional "milestone" ability data.

Aim 2.1: Validation of New Domain-Based Item Banks *(Revised to Year 4 Month 4 – Year 4 Month 9)* – Prospective 1-year data from the DuchenneConnect registry application of newly-derived item banks will be evaluated using techniques described in Aim 1 to confirm that items are responsive to self-reported changes in milestone ability over a time period consistent with design of contemporary clinical trials. Rasch analysis will be repeated to confirm item fit and performance for retained and newly-developed items.

- *Accomplishments and Results:* As noted in the preceding section, construction of a web-based platform for instrument data collection has been completed using RedCap Online Survey resources provided by the UC Davis Clinical and Translational Science Center (CTSC). The system was developed during the initiation of activities in Specific Aim 1.3 to capture data during participant validation interviews, and operational details of the system are provided in the human subject study protocol in Appendix 2. Upon completion of activities in Aim 1.3, the currently live version of the instrument will undergo slight revisions based on participant feedback, with time to complete those revisions is anticipated to take 1-2 days including beta testing. The human subject participation protocol for the DuchenneConnect Registry data collection efforts in Aim 2.1 us currently under development and will be submitted for review by the UC Davis and DoD human subject review groups upon completion of Aim 1.3 activities. Data collection will begin with the assistance of DuchenneConnect immediately upon approval of the human subjects protocol by both institutions. Once data collection is complete, we will conduct a final round of Rasch analysis-based question item calibration and will refine domain item list content to finalize the instrument's item lists.

Aim 2.2: Identification of Item Responsiveness to Group Differences Due to Glucocorticoid Therapy *(Revised to Year 4 Month 7)* – Evaluate the responsiveness of the composite PRO item banks to differences in milestone scores. We will test the hypothesis that functionally-specific mobility and ADL PRO items will be differentially responsive functional "milestone" abilities.

- *Accomplishments and Results:* Using the data from the revised and calibrated item lists on completion of Aim 2.1, we will evaluate responsiveness of the DMD Lifetime Mobility Scale to differentiate between individuals with different levels of functional "milestone" ability. As proof of concept, we recently presented data to the World Muscle Society from the CINRG Duchenne Natural History Study using the POSNA Pediatric Orthopedic Data Collection Instrument (PODCI) where we demonstrated ability of mobility-related domain scores to differentiate between functional "milestone" groups. The POSNA PODCI mobility-related domain scores correlate with 6-minute walk test in ambulatory children and adolescents with Duchenne muscular dystrophy (DMD). Question items address ambulation, transfer and upper limb functional abilities, making the device suitable as an outcome measure in ambulatory and non-ambulatory groups. We compared 5 years of PODCI data from the UCD/CINRG DNHS cohort (n=410), representing >3000 observations from participants from <2-33 years of age. We assigned individuals to a functional "milestone" group representing level of function as previously described (Henricson, 2013). We evaluated items by ordered logistic regression to show differences between milestone groups. We constructed 1-year score differences to identify items that demonstrated change over that time in the group as a whole and in those who lost a functional milestone. 11/11 items in Transfers/Basic Mobility are sensitive to milestone group differences ($p<0.0001$) and show significant 1-year change ($p=0.05$- $p<0.0001$). 8/8 items in Upper Extremity Physical Function are sensitive to milestone group differences ($p<0.0001$) and show significant 1-year change ($p=0.05$- $p<0.0001$). 9/12 items in Sports/Physical Function are sensitive to milestone group difference ($p<0.0001$) and 8/9 milestone-sensitive items show significant 1-year change ($p=0.05$- $p<0.0001$). 1/5 items in Happiness is sensitive to milestone differences ($p<0.0001$). No items in Pain/Comfort are sensitive to milestone differences or 1-year change. Domain scores derived from Transfer/Basic Mobility, Upper Extremity Physical Function, and Sports/Physical Function items are similarly responsive. We conclude that the POSNA PODCI instrument can be used in ambulatory and non-ambulatory DMD. A majority of mobility-related items and their derivative domain scores show differences between functional groups and changes over 1 year in ambulatory and non-ambulatory patients.

- Reference: Henricson E, McDonald CM and the CINRG Investigators. Five-year longitudinal UC Davis CINRG Duchenne Natural History Study (DNHS) data show mobility-focused POSNA PODCI items are sensitive to 12-month disesase progression across all stages of DMD functional ability. Neuromuscular Disorders, October 2015, Volume 25, Supplement 2.

AIM 3: Development of a Computerized Adaptive Testing PRO instrument for use in clinical trials *(Revised to Year 4 Month 7 – Year 4 Month 12)*:
In the fourth year of the project, we will use Aim 2 pilot data to develop a brief computerized adaptive testing (CAT) version of the new composite PRO instrument, and we will make it available to the clinical research community for inclusion in natural history studies and clinical trials for persons with DMD.

- *Accomplishments and Results:* The Cooperative International Neuromuscular Research Group recently transferred it's Coordinating Center from Children's National Medical Center to the Therapeutic Research in Neuromuscular Disorders Solutions (TRiNDS) group, also based in Washington, D.C. The CINRG Duchenne Natural History Study is launching an expanded version of the study that incorporated members of the E.U.-based Prosensa Duchenne Natural History Study (PRO-DMD) at an expanded network of centers worldwide. Plans are currently underway to include the instrument in the new study protocol as a computer-adaptive test for Aim 3 field testing, with data collection from a combined study cohort of up to 500 participants, with the total data collection cohort size be determined initially by use of English as the primary language. Development and approval of the human subject study protocol is slated for Spring of 2018 with data collection to occur during the Summer of 2018.

Aim 3.1: Perform a CAT simulation from data obtained from the comprehensive PRO item banks (Revised to Year 4). A real data simulation approach will be used to investigate the accuracy of each CAT generated from the full-item banks.

Aim 3.2: Establish discriminant and concurrent validity of the CAT version of the composite PRO in parents/ caregivers of DMD subjects (Revised to Year 4 Month 6 – Year 4 Month 12). Evaluation of the ability of the mobility and daily routines full-item banks and the 5-, 10-, and 15-item simulated CATs to discriminate between and among groups of DMD subjects.

What opportunities for training and professional development has the project provided?

Nothing to Report

How were the results disseminated to communities of interest?

Results of Aim 1 activities have been presented in multiple conference proceedings and publications. We presented information on responsiveness of Person Reported Outcomes (PROs) in the CINRG Duchenne Natural History Study at the Duchenne Regulatory Sciences Consortium Workshop in April of 2016. Proceedings of the meeting were recently published in PLoS Currents (Larkindale et al, 2017) and are available to the public via PubMed Central (PMC5300692). Work on the relationship between disease-related functional milestones and pulmonary function characteristics over the lifespan was presented at the Parent Project Muscular Dystrophy Pulmonary Care Workshop (April 2106). The workshop was attended by disease experts, representatives of the pharmaceutical research industry and federal government funding and regulatory agencies. A workshop summary publication is currently under review by the *American Journal of Respiratory and Critical Care Medicine*. Two additional publications are in draft from the CINRG group and highlight the disease milestone concepts developed during Aim 1 of this project. The first paper, *Longitudinal pulmonary function testing outcome measures in Duchenne muscular dystrophy: Long-term natural history with and without glucocorticoids* highlights the relationship between upper limb function and forced vital capacity % predicted scores. The manuscript is currently being submitted to the Neuromuscular Disorders. The second paper, titled *Time to event analysis for the loss of clinically-meaningful milestones in Duchenne muscular dystrophy: The effect of glucocorticoids throughout the lifespan* expands on functional milestone scale items as critical events to assess relative risks of disease progression in steroid-treated and steroid-naïve populations. The paper is being prepared for submission to the New England Journal of Medicine.

What do you plan to do during the next reporting period to accomplish the goals?

During the next reporting period, we will complete item set development and field-test the draft device. Following field administration of the device, we will refine response scales using an iterative Rasch analysis approach and prepare the final device for distribution using a computer adaptive testing design.

IMPACT: Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?

Commonly-employed PROs and Clinically-Reported Outcome Measures (ClinROs) used in DMD research have been noted to apply only to subsets of individuals with respect to age and level of mobility/ability. We have developed prototype mobility question sets that span a range of mobility represented across the lifespan of individuals with DMD, and that are responsive to disease progression over a one-year period of time frequently employed in DMD clinical trials. As previously noted, the functional milestone scales developed here have led to creation of a telephone-based functional assessment for the CINRG Duchenne natural history study. Most recently, we have had the opportunity to compare our upper limb mobility scale concepts with those developed by Drs. Katrin Klingels and Nathalie Goemans from the University of Leuven (Belgium) during development of the DMD Upper Limb PROM (Person Reported Outcome Measure). The UL-PROM consists of 32 items covering four domains of ADL (self-care, food, household function, and communication), and the device's items align in similar fashion to those from the DMD-LMS but with different ceilings and floor levels of assessment. As a result, we are working together to explore the broader range of functional assessment possible through combination of the two tools.

What was the impact on other disciplines?

Nothing to Report

What was the impact on technology transfer?

Data from the CINRG DMD natural history study cohort will provide the basis for development of a "clinical trial-ready" novel lifespan-oriented computer adaptive testing-based PRO measure that has been constructed against a background of comprehensive clinical assessments of strength and function across the DMD lifespan. This PRO measure will be rapidly deployable as a sensitive measure for use in the growing field of DMD clinical trials.

What was the impact on society beyond science and technology?

Nothing to Report

5. **CHANGES/PROBLEMS:** The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change

Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

We experienced delays in the development of the structured interview portion of Aim 1 and electronic tools needed to conduct that aim due to departure of the Evan deBie, the project data manager. We hired a new data manager, who subsequently completed creation of electronic tools and then obtained UC Davis IRB approval for conduct of the required interviews. In addition, the federal funding for the UC Davis/CINRG Duchenne natural history study (DNHS) was completed, and activities were undertaken to extend the conduct of the study under an industry-sponsored consortium. That consortium plan has now been approved, resulting in the closure of the original DNHS study and development of an entirely new study protocol which is scheduled to launch in Spring of 2017. Administration of the DMD-LMS draft tool during the DNHS will begin at that time. Administration of the DMD-LMS in partnership with the DuchenneConnect registry will occur within the same time frame.

Changes that had a significant impact on expenditures

Reductions in staff time (deBie) as previously noted have resulted in under spending the grant award to date. Now that we have returned to being fully staffed, we anticipate a return to originally proposed budget spending levels moving forward. We anticipate that there will be a residual budget at the end of the next year, and we will request a carry forward of unexpended amounts at that time if there are any remaining study activities outstanding.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

Nothing to Report

Significant changes in use or care of vertebrate animals

Nothing to Report

Significant changes in use of biohazards and/or select agents

Nothing to Report

6. **PRODUCTS:** List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications.

  As previously noted, publications include the following:

  1. Larkindale J, Abresch RT, Aviles E, Bronson A, Chin J, Furlong P, Gordish-Dressman H, Habeeb-Louks E, Henricson E, Kroger H, Lynn C, Lynn S, Martin D, Nuckolls G, Rooney W,

Romero K, Sweeney L, Vandenborne K, Walter G, Wolff J, Wong B, McDonald CM and the members of the Duchenne Regulatory Science Consortium, Imaging-DMD Consortium and the CINRG Investigators. Duchenne regulatory science consortium meeting on Duchenne disease progression and progression modeling. PLoS Curr. 2017 Jan 12:9.

2. McDonald CM, Henricson E, Abresch RT, Duong T, Joyce NC, Hu F, Clemens PR, Hoffman EP, Cnaan A, Gordish-Dressman H and the CINRG Investigators. Time to event analysis for the loss of clinically meaningful milestones in Duchenne muscular dystrophy: The effect of glucocorticoids throughout the lifespan. NEJM, In preparation.
3. McDonald CM, Gordish-Dressman H, Henricson E, Duong T, Joyce N, Leinonen M, Hu F, Cnaan A, Abresch RT and the CINRG Investigators. Longitudinal pulmonary function testing outcome measures in Duchenne muscular dystrophy: Long-term natural history study with and without glucocorticoids. Neuromuscular Disorders, *In preparation.*
4. Finder J, Mayer OH, Sheenan D, Sawnani H, Abresch RT, Benditt J, Birnkrant D, Duong T, Henricson E, Kinnett K, Connolly AM, McDonald CM. Pulmonary endpoints in Duchenne muscular dystrophy: a workshop summary. *In preparation.*

Books or other non-periodical, one-time publications.

Nothing to Report

Other publications, conference papers and presentations.

Nothing to Report

- **Website(s) or other Internet site(s)**

Nothing to Report

- **Technologies or techniques**

Nothing to Report

- **Inventions, patent applications, and/or licenses**

Nothing to Report

- **Other Products**

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Craig McDonald, MD (PI) - No Change
Name:	Erik Henricson, MPH (Co-Investigator) - No Change
Name:	Nanette Joyce, DO (Co-Investigator) - No Change
Name:	Anital Bagley, PhD, MPH (Co-Investigator) - No Change

Name:	Evan deBie, BS (Data Manager) – No longer working on the project
Name:	**Corey Owens, MS (Data Manager) – New staff replacing E.D.**
Name:	Erica Goude, MS (Outreach Coordinator) - No Change
Name:	Mary Jane Mulcahey, PhD (Co-Investigator) – No Change

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report

What other organizations were involved as partners?

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to **https://ers.amedd.army.mil** for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.

9. APPENDICES:

Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

Study Protocols

1. DMD-LMS Human Subject Protocol and Electronic Data Collection Instrument
2. UC Davis / CINRG Expanded Duchenne Natural History Study Protocol

Manuscripts

1. Larkindale J, Abresch RT, Aviles E, Bronson A, Chin J, Furlong P, Gordish-Dressman H, Habeeb-Louks E, Henricson E, Kroger H, Lynn C, Lynn S, Martin D, Nuckolls G, Rooney W, Romero K, Sweeney L, Vandenborne K, Walter G, Wolff J, Wong B, McDonald CM and the members of the Duchenne Regulatory Science Consortium, Imaging-DMD Consortium and the CINRG Investigators. Duchenne regulatory science consortium meeting on Duchenne disease progression and progression modeling. PLoS Curr. 2017 Jan 12:9.

Initial Development of the Duchenne Muscular Dystrophy Lifetime Mobility Scale by Rasch Analysis

Erik Henricson, PhD

Abstract

The Duchenne Muscular Dystrophy Lifetime Mobility Scale (DMD-LMS) is an instrument currently in development by CINRG investigators. The DMD-LMS is comprised of three subdomains representing 1) walking and moving, 2) transfers and trunk stability, and 3) carrying, moving and handling objects measuring from early ambulatory to late non-ambulatory stages of disease, and each subdomain is scored out of 100 points. The DMD-LMS, developed using Rasch analysis methods, has demonstrated internal validity and is capable of differentiating between steroid-treated and non-treated groups, between functional "milestone" groups, and has demonstrated significant change over one year across all stages of disease.

Initial Development and Characteristics of the DMD Lifetime Mobility Scale (DMD-LMS)

Introduction

In our third study, we combine our "milestone" scale from Study 1 with evaluation of "clinically-meaningful" PRO item change over time to evaluate PRO items that show clinically-important differences in response to either disease progress over one year or loss of a milestone. Using the resulting set of PRO items, we will construct item banks based on the WHO-ICF domains representing the basic health condition, body structure and function, activities and participation, personal and environmental factors (Figure V.1).

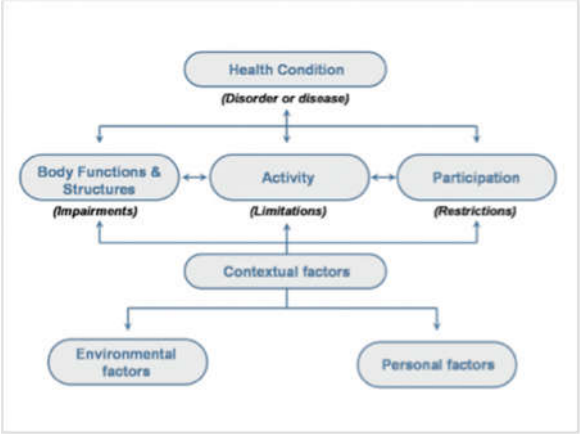


Figure V.1: Duchenne Natural History Study Structure - The WHO ICF Model Encourages Study of Multi-Level Interactions

The past several years have seen a marked increased interest by pharmaceutical companies in conducting ground-breaking research and development into effective treatment agents for DMD. Therapeutic approaches under development for clinical trials in DMD include antisense oligonucleotide (AON) exon skipping therapies, gene therapy strategies, stem cell therapies, as well as a host of small-molecule therapies (e.g. compounds that induce read-through of premature stop-codon mutations, promotion of muscle growth via myostatin inhibition, utrophin upregulation, and steroid analogs with improved side effect profiles). While these therapeutic approaches will not be curative, there is significant hope that new therapies on the horizon will significantly alter disease progression, improve function, and improve quality of life. Ideal clinical endpoints used for future clinical trials need to be clinically meaningful both with regard to a) patient-reported outcome measures focused on well-being and health-related quality of life and b) clinically meaningful milestones such as loss of ambulation, self-feeding, and reliance on non-invasive ventilation.

Here we will use 4-7 years of existing PRO data from our WHO-ICF-based Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study to develop "item banks" of questions that can detect both differences due to variation in functional abilities and that are capable of detecting changes over a one-year period of time. An *item bank* comprises items that define and quantify common themes and thus provide an operational definition of a latent trait (1). In the future, these item banks will provide the foundation for testing using either dynamic computerized adaptive testing (CAT) or static testing using multiple created short-forms. CAT is a process of test administration in which items are selected on the basis of the patients' responses to previously administered items (2). This process uses an algorithm to estimate *person level* to choose the next best item and administer the test under specifications such as content coverage and scale length. This capacity to measure all patients on the same continuum, even if they have not been presented any items in common, offers a scale that is individually tailored to each patient.

Specific Aims

Using the CINRG DMD NHS data, we will use Rasch analysis techniques to analyze PRO measure item responses to develop a novel DMD-specific composite PRO measure that measure multiple domains and spans the entire spectrum of DMD severity and progression. We will conduct a retrospective analysis of 4-7 years of longitudinal multicenter WHO ICF-based data (PODCI, PedsQL, SF-36, Life Satisfaction Index, DMD Sleep Quality Index, WHO-QoL, NeuroQoL) on health conditions, body structure and function, activity, participation, personal and environmental factors, and person-reported quality of life (Figure V.2) from patients and parents of the 420 families enrolled in the CINRG Duchenne natural history study.

Figure V.2: WHO ICF Elements in the UCD/CINRG Duchenne Natural History Study

CINRG Duchenne Natural History Study
WHO ICF Model Elements

Health Condition	Body Structure and Function	Activity	Participation	Personal Factors	Environmental Factors
• Molecular Diagnostics • DNA for SNP / GWAS analysis • Dystrophin Immuno-histochemistry • Medical Status Review • Steroid therapy	• Strength • Pulmonary Function • Anthropometrics • Vital signs • Body composition • Range of motion • Spine deformity • Cardiac evaluation	• Functional testing • Timed motor performance • 6-minute walk • 9-hole peg • North Star • EK Scale	• PedsQL • PedsQL Neuromuscular Module • POSNA • NeuroQoL • WHO QoL Brief • SF-36 • Pittsburgh Sleep Quality Index	• PedsQL • Life Satisfaction Index • Sociodemographic Data (NIFD Questionnaire) • Educational attainment	• Health Service Utilization • WHO-QoL • Sociodemographic Data (NIFD Questionnaire) • Community Accessability • Educational environment

With over 1600 person-years of follow up available from this cohort, we will address the following specific aims:

Aim 1: Development of draft WHO-ICF domain-based lists using PRO items from the UC Davis/CINRG Duchene Natural History Study (DNHS). Using individuals items from the POSNA PODCI, PedsQL, WHO-QoL, SF-36, NeuroQoL, Life Satisfaction Index and Pittsburgh Sleep Quality Index we will assign each to domain-based lists representing latent constructs representing the WHO-ICF domains for Mobility, General Tasks and Demands, Interpersonal Relationships, Community Social and Civic Life, Major Life Areas, Mental (Psychological) Functions, Pain, Neuromuscular and Movement Functions, Support and Relationships, and Services Systems and Policies. Following assignment, the domain-based lists will be circulated to a panel of expert reviewers. Mis-fit items will be discussed by the review panel members, who will determine final domain list assignments.

Aim 2: Evaluation of item responsiveness to differences in disease stage and steroid treatment. Using all available PRO data, we will evaluate item responses across domains to refine domain-specific item banks for future use in composite PRO measures. We will evaluate responsiveness of PRO items at differing levels of clinically-meaningful "milestone" function represented by ability to stand from supine, climb stairs, rise from a chair, ambulate independently, raise a hand to the mouth for feeding, and the requirements for mechanical cough assistance for airway clearance (defined as having a forced vital capacity >50% of predicted values for age). We will evaluate item change over a one-year period of time consistent with current clinical trial designs.

Aim 3: Rasch Analysis to evaluate latent construct validity and item content. We will use Rasch Unidimensional Measurement Model (RUMM2030) software to evaluate domain list item responses to examine whether items are clinically meaningful, if they are targeted across the observable range of phenotype and are independent, whether individual and item responses fit within an overall model and whether the resulting scale reliably identifies differences between individuals. This will occur in a two-step process, with initial evaluation, followed by item list refinement and re-evaluation.

Aim 4: Validation of final domain-based item banks. Using Rasch analysis-based validity testing methods described in Aim 3, we will evaluate the final domain-based item lists to determine their ability to quantitatively measure their proposed latent constructs. From the output, we will construct a 0-100 point linear logit-transformed scoring scale for each domain-based bank.

Methods

Timing and Content of Assessments

Because the DNHS is a long-term study, procedures are essentially the same every time the participant visits the clinic for their annual checkup. This study has been designed so that assessments are completed according to **Table V.1**. All ambulant study subjects, during Year 1, should complete study visits every 3 months at Month 1, Month 3, Month 6, Month 9 and Month 12. All non-ambulant study subjects, the optimal Year 1 visit schedule is every 3 months. However, the first year visit schedule should reflect their local

standard of care practice. For those participating sites where standard of care occurs every 6 months, study visits will only be required every six months: Month 1, Month 6, and Month 12.

TABLE V.1: Schedule of Study Visits by Year

Calendar Year by Month	Baseline	Month 3	Month 6	Month 9	Month 12
Year 1: Ambulant	x	X	x	x	x
Year 1: Non-ambulant	x		x		x
Year 2			x		x
Year 3					x
Year 4					x
Year 5					x
Subsequent Years					x

Some assessments are age- or disease stage-specific, and so will only be completed at some visits. Details on assessments are provided below and include age- and disease stage-specific guidelines.

Anthropometrics (All ages): Anthropometric measures will include standing height, weight, and ulnar length. Standing height will only be measured for individuals who are able to stand unassisted. Specific methods are outlined in the CQMS User's Manual Appendix.

Timed Function Testing (Age 2 as able and up): Timed motor performance (e.g. time to walk 10 m., time to climb 4 stairs and time to stand from supine from floor) tests will follow the protocol reported by our group (3, 4). Specific methods are outlined in the CQMS User's Manual Appendix. If the subject is unable to cooperate with the examiner, the test should be skipped and re-introduced at the next visit.

Brooke upper extremity scale and Vignos lower extremity scale (Age 4 and older, as able): The functional classification used by CINRG utilizes a scale modified from the upper extremity scale reported by Brooke et al. (5) and the lower extremity scales used by Vignos et al. (6). The functional grades consist of six levels of function for the upper extremities. For participants able to perform the first level they will also be asked to complete this level with small weights. The lower extremity includes eleven levels. If the subject is unable to cooperate with the examiner, the test should be skipped and re-introduced at the next visit. Specific methods are outlined in the CQMS User's Manual Appendix.

Pulmonary Function Testing (PFT) (Age 6 as able and up): Pulmonary Function Tests (PFT) will be done in the standard fashion using the methods outlined in the CQMS User's Manual Appendix. PFTs will be performed in sitting and supine. PFTs will include maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), forced vital capacity (FVC), forced expiratory volume 1 (FEV1), peak expiratory flow (PEF), and peak cough expiratory flow (PCEF). If the subject is unable to cooperate with the examiner, the test should be skipped and re-introduced at the next visit.

Review of Systems – Physician Visit: Physicians will conduct a detailed review of systems that will include a physical and neurological examination and medical history. This will be aided by review of the completed intake or annual review of systems form packet. Following the physicians review of systems, participants or guardians should review past month medication use with either the physician or study coordinator using the medication form included in the intake or annual review of systems form packet. Physicians or study coordinators should attempt to gather trade/generic name, dose, route, frequency and indication for each medication that is reported on the form. Participants or guardians should bring all medications to the visit with them to facilitate this review.

POSNA (Every visit, Ages 5 and older): The Pediatric Orthopaedic Functional Health Questionnaire of the Pediatric Orthopaedic Society of North America (POSNA) was developed by the POSNA in 1994 (7, 8). The POSNA assessment is designed to measure actual functional levels of pediatric orthopedic patients. The primary scales of the instrument include assessment of upper extremity function, transfers/mobility, physical function and sports, comfort/pain, happiness and satisfaction and expectations for treatment. Both parent proxy and adolescent self-report forms have been validated. This is a self-administered questionnaire. Parents/guardians will complete a proxy assessment for all children under 18. Teens (11-17) will complete a self-report assessment.

PedsQL (5-17) (Every visit. All Participants): Pediatric Quality of Life Inventory, Version 4 (Peds QL 4.0) (9-11). The Pediatric Quality of Life (PedsQL) Inventory is a self-report measure designed to measure core health dimensions in children from 5 to 17 years old. The measure consists of 23 items in four scales: physical functioning, emotional functioning, social functioning, and school functioning. Parents/guardians will complete a proxy assessment for all children under 18. Teens (11-17) will complete a self-report assessment.

WHO QOL Brief (Every visit. Adult Subject 18 years and older): The World Health Organization Quality of Life Assessment – Brief (The WHO QOL Group, Geneva) has been widely used to assess individuals perceptions on their quality of life with respect to culture, values, goals, standards and concerns. The 26-item assessment covers contains major domains that assess physical health, psychological health, social relationships and environment (12, 13). This is a self-administered questionnaire.

Life Satisfaction Index (Every visit. Teens (11-17) and Adults with DMD): Life Satisfaction Index for Adolescents (14). The Life Satisfaction Index for Adolescents consists of five domains: general well being, interpersonal relationships, personal development, personal fulfillment, and leisure and recreation. Each item is ranked on a five-point rating scale. Domain scores and a total score are derived.

DMD Sleep Quality Index (Every visit. Teens (11-17) and Adults with DMD and Parent/Guardian (proxy)): The DMD Sleep Quality Index is an adaptation of the Pittsburgh Sleep Quality Index (PSQI) (15). The PSQI is self rated and assesses sleep quality over the preceding 1 month. Major domains include subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of medication and daytime dysfunction. The DMD-related modification incorporates items associated with common DMD-related orthopedic and respiratory complications that are thought to impact sleep in affected individuals.

Pediatric and Adult NeuroQOL: Adult and child/adolescent versions of the NeuroQOL will be administered at baseline and each annual visit (16-18). Participants will be asked a series of Likert-scale questions covering domains including Mobility/Ambulation, Activities of Daily Living/Upper Extremity, Social Health, Emotional Health, Stigma, Perceived Cognitive Function, Fatigue and Pain domains. Both parallel child self-report (for ages > 10) and parent proxy-report formats (for all subjects) will be used in pediatric populations. The same domains from the adult version of the survey will be used in participants at least 18 years of age. The item responses are compared to population response frequencies using Item response theory thus yielding a z-score for each response and a standard score with mean of 50 and standard deviation of 10.

Analysis of Data

Classification of Question Items to WHO-ICF Categories: Individual question items from each instrument were classified by a group of expert reviewers according to WHO-ICF categories and subcategories for Part B: Function, Part D: Activities and Participation, and Part E: Environmental Factors. Where applicable, questions were classified into multiple categories. When there were disagreements regarding category assignment, items were discussed until consensus was reached.

Principle Component Factor Analysis and Scale Reliability: Using the raw item response scores for items assigned by expert review to each WHO-ICF subcategory, we conducted confirmatory principle components factor analysis to evaluate whether items were likely to represent a "pure" construct. To evaluate reliability of these item lists, we calculated Cronbach's alpha statistic.

Analysis of Item Sensitivity to Disease Progression and One Year Change: We used the previously described 6-level composite of individual functional "milestone" tasks, combining the results from the ability to perform the timed function tests as well as the Brooke and Vignos functional scales (19). To further differentiate among non-ambulatory individuals with limited upper limb ability, we added a seventh level representing limited respiratory function with a forced vital capacity of <30% indicating a need for full-time mechanical ventilation. The levels of this composite scale are: (0) able to complete all 3 timed tests; (1) unable to stand from supine but performed the 4 step climb and the walk; (2) unable to climb 4 standard stairs, can walk 10 meters, Vignos grade <5; (3) cannot rise from chair, but can walk 10 meters, Vignos scale <7; (4) cannot walk 10 m, but can raise hand to mouth, Brooke <5; (5) unable to raise a hand to the mouth, Brooke scale 5 or 6; (6) unable to raise a hand to the mouth, Brooke scale 5 or 6 and FVCP<30%. We then grouped participants according to whether or not they had changed milestone grades over the one-year period between evaluations. We defined a "successful" instrument or instrument subscale as one that: a) differentiated between milestone groups; b) showed significant change over a one-year period of time, and c) was deemed "clinically significant" by meeting or exceeding change of 1/3 the standard deviation of the measure for either the group as a whole or among individuals who showed a change in milestone scale score indicating loss of a key functional ability.

Psychometric Evaluation using Rasch Analysis: Rasch analysis is form of item response theory that is used as an alternative to classical test theory methods of determining reliability and validity of scale-based measurement tools, which have been criticized as "weak" measurements because of lack of continuous measures, scale-dependent scores, lack of sensitivity to change and floor and ceiling effects that hamper interpretation of scores (20). Rasch analysis provides a "strong" construct-based approach to assessing responses to question items by individuals in a given patient population whereby item response probabilities are modelled for each individual response item and individuals are placed according to their response characteristics on a continuous scale representing fixed intervals across a phenotypic range. Analysis using the Rasch Unidimensional Measurement Model (RUMM2030) software aids in evaluation of instrument responses to examine whether items are clinically meaningful, if they are targeted across the observable range of phenotype and are independent, that individual and item responses fit within an overall model and whether the resulting scale reliably identifies differences between individuals.

Clinical Meaning: Clinical meaningfulness is assessed through ordering of locations of items and response thresholds in terms of ascending or descending difficulty across the population studied, and is displayed on the threshold ordering map. We expected that

items would locate in a way that is consistent with previous clinical natural history observations of ordinal loss of function in DMD patients (19).

Targeting: Targeting is assessed by evaluating item locations relative to the locations of individuals along the continuum representing good to poor function, and is displayed on the person-item threshold distribution. Appropriately targeted measures will demonstrate an equally distributed range of item thresholds that extends beyond the location of all individuals in the studied population. This would indicate freedom from floor and ceiling effects of the measurement tool.

Dependency: Dependency is assessed by evaluating the correlation coefficients of residual fit values generated by comparing aggregate actual responses to modelled responses. Items with a high degree of correlation (defined here as >0.4), and thus a high degree of dependency often show that response on one item directly dictates response on another.

Fit: Fit can be assessed for both items and individuals by calculating residual values comparing actual responses to modelled responses for an individual across items or for an item across individuals. The lower the residual value and the higher the p-value for inclusion in the model, the better the fit. For individual items and individuals, a residual value of $<|3.0|$ is considered acceptable, with acceptance for inclusion in a model set here at $p>0.01$, where items with high residuals exhibit less fit and statistically significant p-values indicate that observed variance is non-random.

Person Separation Index: The Person Separation Index (PSI) indicates the power of overall ability of a model construct to individuate between respondents. A PSI value of >0.8 is generally accepted as "good" overall model fit.

Iterative Approach to Model Construction: Datasets were constructed for each domain construct list using all clinically-responsive items as determined according to the item sensitivity analysis section listed above. The approach to data analysis was to conduct an initial analysis based on all items in the data set. The initial analysis generated information on overall model fit, individual item fit, item response threshold order and item dependency. Results from the first-pass analyses were used to determine which overall domain and subdomain set demonstrated the highest initial model fit based on the available responses across different age groups. For the selected domain / subset group, a secondary analysis including item rescoring and item selection was conducted. For the secondary analysis, items that demonstrated disordered item response thresholds were evaluated to determine whether any response items could be condensed in a clinically meaningful way, and were recoded if that was possible, or otherwise were not retained. Items that demonstrated a high degree of correlation and dependency were examined to determine whether they represented a similar construct (i.e. they are measuring similar or different levels of the same thing). Where such items were considered duplicative and items were administered consistently across the sample group, only the most clinically representative item was retained for further analysis. For similar items that were administered only to specific sub-populations (ie. only children for one question, only teens for it's similar counterpart), items were retained but need for future consolidation with one unified question was noted. Then data was re-analyzed using only retained items to determine whether model characteristics improved.

Results

Study Population: Four hundred and ten patient-parent/guardian pairs completed survey instruments and clinical evaluation testing. Full details on the content and timing of visits and the overall subject population have been previously published (19, 21). Participants represented a wide range of ages representative of the disease (age at initial visit 11.3[5.7] years, range 4 – 28 years). The number of completed visits per participant ranged from 1 to 13 (mean 5[3]) with follow-up in some participants to month 96, for a total of 3066 completed visits. At baseline 125 (30%) of participants were glucocorticoid steroid-naïve, 49 (12%) were previous steroid users, and 236 (58%) were steroid users. At baseline 253 (62%) were ambulatory, and 47 (11%) had a forced vital capacity <30% of predicted for age.

Grouping Question Items by WHO-ICF Domains: Using a group of expert reviewers, we classified 367 question items according to the WHO-ICF domains for Function (Part B), Activities and Participation (Part D) and Environmental Factors (Part E), with each question being considered for inclusion under each construct. A summary of the number of items included in each construct and subdomain, by original instrument is included as Table V.2. When classified under the Function construct, 142 items were assigned to the Mental Function subdomain, 10 to the Sensory Functions and Pain subdomain, 8 to the Functions of the Hematological, Immunological and Respiratory Systems subdomain, 148 to Neuromusculoskeletal and Movement-Related Functions subdomain, and one to the Functions of the Skin and Related Structures subdomain. Items were further subclassified under each subdomain as noted in Table V.2. When classified under the Activities and Participation construct, 12 items were assigned to the Learning and Applying Knowledge subdomain, 20 to General Tasks and Demands, 12 to Communications, 110 to Mobility, 60 to Self-Care, two to domestic life, 28 to Interpersonal Interactions and Relationships, 10 to Major Life Areas, and 26 to Community, Social and Civic Life. Under the Neuromusculoskeletal and Movement-Related Functions subdomain, we created further sub-classifications that represent domains from the Performance of the Upper Limb (PUL) (22) and North Star Ambulatory Assessment (NSAA) (23) clinical evalutions with the goal of subdividing self-report tasks according to existing models of upper limb function and ambulatory mobility. When classified under the Environmental Factors construct, 30 items were assigned to the Products and Technology subdomain, 10 to Natural Environment and Human-Made Changes to the Environment, 14 to Support and Relationships, two to attitudes, and 27 to Services, Systems and Policies.

Item Sensitivity to One-Year Change and Disease Progression: We evaluated each question item to evaluate whether it was able to detect differences between individuals of different functional milestone groups, and its ability to demonstrate significant change in a one-year period of time consistent with the duration of most contemporary clinical trials. Taken together, item responsiveness screening yielded a list of 138 of the original 367 question items (37.6%). A summary of the numbers and percent of sensitive question items by WHO-ICF domain/subdomain and instrument is presented in Table V.2. In the Function construct, only a very small number of questions in the Mental Functions subdomain (0.4%) and none of the items in the Functions of the Skin and Related Structures subdomain met criteria for being responsive. Approximately half of the items in the Sensory Functions and Pain (40%) and Functions of the Cardiovascular, Hematological, Immunological and Respiratory Systems subdomains (50%) demonstrated responsiveness. Three quarters (75%) of items assigned to the Neuromuscular and Movement-Related Functions subdomain demonstrated responsiveness. In the Activities and Participation construct, relatively small percentages of items demonstrated responsiveness if the Learning and Applying Knowledge subdomain (25%), General Tasks and Demands (5%), Interpersonal Interactions and Relationships (11%), Major Life Areas (0%), and Community, Social and Civic Life (27%). Approximately half of items in the Communication subdomain (50%), Self Care (53%) and Domestic Life (50%) demonstrated responsiveness, although the latter was comprised of a single item. Of 110 items initially assigned to the Mobility subdomain, 74 (67%) demonstrated responsiveness to disease stage and progression over time. The percentage of responsive items in the Environmental Factors construct subdomains varied, representing none (0%) in Attitudes, 11% in Services, Systems and Policies, 21% in Support and Relationships, 30% in Natural Environment and Human-Made Changes to the Environment, and 50% in Products and Technology.

Table V.2

Responsive Items / All Items by WHO-ICF Domain and Instrument (#/%)									
Domain/Subdomain	**LSI-A**	**NeuroQoL**	**PedsQL**	**PedsQL NMM**	**POSNA PODCI**	**PSQI**	**SF-36**	**WHO-QoL**	**All Instruments**
ICF Part B: Function									
Subdomain: Mental Function									***6/142 (0.4%)***
Intellectual Function	0/3 (0%)		0/1 (0%)						0/4 (0%)
Temperament and Personality Functions	0/9 (0%)		0/1 (0%)		0/1 (0%)				0/11 (0%)
Energy and Drive Functions	0/4 (0%)	0/17 (0%)	**1/1 (100%)**	0/2 (0%)	0/2 (0%)	0/1 (0%)	0/4 (0%)	0/1 (0%)	**1/32 (3%)**
Sleep Functions		0/1 (0%)	0/1 (0%)	**1/1 (100%)**		**3/10 (30%)**			**4/13 (31%)**
Attention Functions			0/1 (0%)					0/1 (0%)	0/2 (0%)
Memory Functions			0/1 (0%)						0/1 (0%)
Emotional Functions: Anxiety		0/13 (0%)	0/1 (0%)				0/2 (0%)		0/16 (0%)
Emotional Functions: Depression	0/2 (0%)	0/13 (0%)	0/1 (0%)				0/3 (0%)	0/2 (0%)	0/21 (0%)
Emotional Functions: Fear	0/1 (0%)	0/3 (0%)	0/1 (0%)						0/5 (0%)
Emotional Functions: Frustration	0/2 (0%)		0/1 (0%)						0 (0%)
Emotional Functions: Satisfaction	0/14 (0%)	0/1 (0%)			**1/5 (20%)**			0/14 (0%)	**1/34 (3%)**
Subdomain: Sensory Functions and Pain									***4/10 (40%)***
Sensory Functions and Pain			**1/1 (100%)**	**1/2 (50%)**	0/3 (0%)	**2/3 (66%)**		0/1 (0%)	**4/10 (40%)**
Subdomain: Functions of the Cardiovascular, Hematological, Immunological and Respiratory Systems									***4/8 (50%)***
Functions of the Hematological and Immunological Systems				**1/2 (50%)**		0/2 (0%)			**1/8 (25%)**
Functions of the Respiratory System				**1/2 (50%)**					**1/2 (50%)**
Functons Related to the Digestive System				**1/1 (100%)**					**1/1 (100%)**
Functions Related to Metabolism and the Endocrine System				**1/1 (100%)**					**1/1 (100%)**
Subdomain: Neuromusculoskeletal and Movement-Related Functions									***112/148 (75%)***
PUL High Level: Shoulder Dimension		**7/11 (64%)**	**1/1 (100%)**		**6/8 (75%)**				**14/20 (70%)**
PUL Mid-Level: Elbow Dimension		**14/18 (77%)**		0/1 (0%)	**3/3 (100%)**				**17/22 (22%)**
PUL Distal-Level: Wrist and Finger Dimension		**8/11 (73%)**		**2/2 (100%)**	**1/1 (100%)**				**11/14 (79%)**
Complex: Standing from Supine		**2/3 (66%)**							**2/3 (67%)**
Complex: Standing from Seated		**6/7 (86%)**			**1/1 (100%)**				**7/8 (88%)**
Complex: Transfers		**7/10 (70%)**		**1/1 (100%)**	**1/1 (100%)**				**9/12 (75%)**
Head/Neck		**1/1 (100%)**							**1/1 (100%)**
Trunk: Standing		**6/7 (86%)**	**1/1 (100%)**	**1/1 (100%)**	**1/1 (100%)**				**9/10 (90%)**
Trunk: Sitting		**6/8 (75%)**			**4/4 (100%)**				**12/12 (100%)**
LL: Running		0/6 (0%)	**2/2 (100%)**		**4/5 (80%)**				**6/13 (46%)**
LL: Climbing		**2/7 (29%)**			**3/3 (100%)**				**5/10 (50%)**
LL: Walking		**12/15 (80%)**	**2/3 (66%)**		**5/5 (100%)**				**19/23 (83%)**
Subdomain: Functions of the Skin and Related Structures									***0/1 (0%)***
Functions of the Skin and Related Structures				0/1 (0%)					0/1 (0%)
ICF Part D: Activities and Participation									
Subdomain: Learning and Applying Knowledge									***3/12 (25%)***
Learning and Applying Knowledge	0/3 (0%)	0/2 (0%)	**2/5 (40%)**		**1/1 (100%)**			0/1 (0%)	**3/12 (25%)**
Subdomain: General Tasks and Demands									***1/20 (5%)***
Undertaking Multiple Tasks	0/1 (0%)	0/3 (0%)							0/4 (0%)
Carrying Out a Daily Routine	0/3 (0%)	0/1 (0%)		**1/1 (100%)**	0/2 (0%)	0/2 (0%)		0/6 (0%)	**1/15 (7%)**
Handling Stress and Other Psychological Demands		0/1 (0%)							0/1 (0%)
Subdomain: Communication									***6/12 (50%)***
Communication	0/1 (0%)	**5/7 (72%)**		0/3 (0%)	**1/1 (100%)**				**6/12 (50%)**
Subdomain: Mobility									***74/110 (67%)***
Changing and Maintaining Body Position		**19/21 (90%)**		**1/1 (100%)**	**8/8 (100%)**				**28/30 (93%)**
Carrying, Moving and Handling Objects		**13/24 (54%)**	**1/1 (100%)**	**2/2 (100%)**	**4/4 (100%)**				**20/31 (65%)**
Walking and Moving		**13/29 (45%)**	**2/2 (100%)**		**10/12 (83%)**			0/1 (0%)	**25/44 (57%)**
Moving Around Using Transportation		0/3 (0%)			**1/1 (100%)**			0/1 (0%)	**1/5 (20%)**
Subdomain: Self-Care									***32/60 (53%)***
Washing Onesself		**6/8 (75%)**	**1/1 (100%)**	**1/1 (100%)**					**8/10 (80%)**
Caring for Body Parts	0/1 (0%)	**3/4 (75%)**			**1/1 (100%)**			0/1 (0%)	**4/7 (57%)**
Toileting		**4/5 (80%)**		**1/1 (100%)**					**5/6 (83%)**
Dressing		**7/8 (88%)**			**2/2 (100%)**				**9/10 (90%)**
Eating		**1/2 (50%)**		0/1 (0%)	**1/1 (100%)**				**2/4 (50%)**
Drinking		**1/1 (100%)**							**1/1 (100%)**
Looking After One's Health	0/1 (0%)			0/1 (0%)	0/6 (0%)	**3/9 (33%)**		0/5 (0%)	**3/22 (14%)**
Subdomain: Domestic Life									***1/2 (50%)***
Domestic Life		0/1 (0%)	**1/1 (100%)**						**1/2 (50%)**
Subdomain: Interpersonal Interactions and Relationships									***3/28 (11%)***
Informal Social Relationships	0/3 (0%)	**1/6 (17%)**	0/5 (0%)		0/3 (0%)			0/2 (0%)	**1/19 (5%)**
Family Relationships	0/4 (0%)			**2/3 (66%)**					**2/7 (29%)**
Intimate Relationships	0/1 (0%)							0/1 (0%)	0/2 (0%)
Subdomain: Major Life Areas									***0/10 (0%)***
Major Life Areas	0/9 (0%)							0/1 (0%)	0/10 (0%)
Subdomain: Community, Social and Civic Life									***7/26 (27%)***
Community Life	0/2 (0%)	0/2 (0%)		**1/1 (100%)**					**1/5 (20%)**
Recreation and Leisure	0/8 (0%)	0/4 (0%)	**1/1 (100%)**	**1/1 (100%)**	**4/6 (66%)**			0/1 (0%)	**6/21 (29%)**
ICF Part E: Environmental Factors									
Subdomain: Products and Technology									***15/30 (50%)***
Products and Technology	0/1 (0%)	**8/17 (47%)**		**2/3 (66%)**	**5/7 (71%)**	0/1 (0%)		0/1 (0%)	**15/30 (50%)**
Subdomain: Natural Environment and Human-Made Changes to the Environment									***3/10 (30%)***
Natural Environment and Human-Made Changes to Environment		**3/10 (30%)**							**3/10 (30%)**
Subdomain: Support and Relationships									***3/14 (21%)***
Support and Relationships	0/8 (0%)			**3/3 (100%)**				0/3 (0%)	**3/14 (21%)**
Subdomain: Attitudes									***0/2 (0%)***
Attitudes	0/1 (0%)			0/1 (0%)					0/2 (0%)
Subdomain: Services, Systems and Policies									***3/27 (11%)***
Services, Systems and Policies	0/12 (0%)		**2/3 (66%)**	0/3 (0%)	**1/1 (100%)**			0/8 (0%)	**3/27 (11%)**

** Note: A total of n=366 question items were reviewed. Each question was assigned to subdomains in Part B, Part D and Part E as applicable.*

Characteristics of Domain-Based Item Lists and Selection of Mobility Scales

Table V.3: Principle component factor list by WHO-ICF domain and subdomain

Factor List by Domain / Subdomain		
ICF Part B: Function		
Subdomain: Mental Function	Sleep Functions	F1 - Nightime Awakening
Subdomain: Sensory Functions and Pain	Sensory Functions and Pain	F1 - Pain
Subdomain: Neuromusculoskeletal and Movement-Related Functions	PUL High Level: Shoulder Dimension	F1 - Unweighted or Range of Motion F2 - Weighted or Strength
	PUL Mid-Level: Elbow Dimension	F1 - Fine Motor and Reaching the Face F2 - Dressing F3 - Bimanual Strength Tasks
	PUL Distal-Level: Wrist and Finger Dimension	F1 - Hand Weakness F2 - Pointing F3 - Writing F4 - Holding Objects F5 - Email/Texting (Key Use)
	Complex: Standing from Seated	F1 - Standing from a Chair F2 - Standing from a Chair without Aid of Arms F3 - Standing from a Bathtub
	Complex: Transfers	F1 - Changing Positions in Bed F2 - Getting off the Toilet F3 - Wheelchair Transfers
	Trunk: Standing	F1 - Low to High Bending Reach F2 - Toilet and Sink Standing F3 - Bathing (Bath or Shower) F4 - Bathing (Shower Only)
	Trunk: Sitting	F1 - Bending at the Waist / Torso Control F2 - Torso Control - Toilet or Wheel Chair F3 - Unsupported Sitting with Time Element F4 - Unsupported Sitting F5 - Bathing Ability (Bathtub)
	LL: Running	F1-F3 - Sports Participation and Running (Not distinct factors)
	LL: Climbing	F1 - Long Duration or High Climbs F2 - Short Duration or Low Climbs
	LL: Walking	F1 - Long Duration Walks F2 - Short Walks and Uneven Surfaces F3 - Long Distance Walks (Ability to Do) F4 - Balance and Falls F5 - Long Distance Walks (Perception of Problem)
ICF Part D: Activities and Participation		
Subdomain: Learning and Applying Knowledge	Learning and Applying Knowledge	F1 - Missing School
Subdomain: Communication	Communication	F1 - Pointing and Manipulating Keyboards F2 - Writing F3 - Texting and Email (Behavioral Component)
Subdomain: Mobility	Changing and Maintaining Body Position	F1 - Transfers and Positional Changes F2 - Standing from Seated or Supine F3 - Sitting
	Carrying, Moving and Handling Objects	F1 - Tasks that Require Strength F2 - Tasks that Require Manual Dexterity F3 - Wheelchair-Related Manual Tasks
Subdomain: Self-Care	Washing Onesself	F1 - Washing, Drying in Bath or Shower F2 - Bathing, Bathtub Only F3 - Transfer to Bathtub
	Caring for Body Parts	F1 - Combing Hair, Brushing Teeth
	Toileting	F1 - Transfering to and From Toilet F2 - Self-Care on Toilet
	Dressing	F1 - Getting Dressed and Undressed F2 - Working Buttons and Zippers
Subdomain: Community, Social and Civic Life	Recreation and Leisure	F1-F3 Participation in Sports and Recreation (Not distinct factors)
ICF Part E: Environmental Factors		
Subdomain: Natural Environment and Human-Made Changes to the Environment	Natural Environment and Human-Made Changes to Environment	F1 - Ambulating Short Distances
Subdomain: Support and Relationships	Support and Relationships	F1 - Family Stress and Coping

Principle Components Analysis: Following construction of the expert review-generated WHO-ICH-based responsive item lists, we examined each set of items using confirmatory principal components factor analysis in order to determine whether there were any potential underlying sub-constructs. A summary of factor analysis results is shown in Table V.3. Lists for sleep, pain, school function, caring for body parts, recreation and leisure, and family relationships all demonstrated an appreciable level of unidimensionality. However, most of the lists demonstrated multidimensionality even within groups of items that are frequently grouped together in clinical outcome measure tools. This suggests that even when question items are subdivided into categories according to the WHO-ICF model, there may be multiple underlying "pure" or latent constructs that could further elaborate on those subdivisions.

First Pass Rasch Analysis

We conducted a first-pass Rasch analysis of disease progression-responsive questions in each domain construct question list. Specific analysis results are listed in Appendix V.1 (ICF Domain Construct Question List and Analyses) and results are summarized in Table V.4. Twenty-nine disease progression-responsive question lists were evaluated under the ICF Part B Structure and Function Domain. Twelve of 29 lists contained enough responsive items to conduct an initial Rasch analysis, with 10 of the lists representing various neuromusculoskeletal and movement-related physical functions, 1 representing sensory functions and pain, and 1 representing sleep functions. Only three of those 12 lists demonstrated a somewhat acceptable person separation index of >0.7. and none of the lists covered an acceptable spectrum of disease severity from early ambulatory to late non-ambulatory patients. Twenty-three disease progression-responsive question lists were evaluated under the ICF Part D Activities and Participation Domain. Thirteen of 23 lists contained enough responsive items to conduct an initial Rasch Analysis. Of those 13 lists, 1 represented learning and applying knowledge, 1 represented communication, 3 represented mobility, 6 represented self care, 1 represented interpersonal interactions and relationships, and 1 represented recreation and leisure activities. Only the mobility domains demonstrated acceptable person-separation indices of 0.7-0.887, but question lists covered the spectrum of disease severity from early ambulatory to late non-ambulatory patients. Five disease progression-responsive question lists were evaluated under the ICF Part E Environmental Factors Domain. Three of 5 lists contained enough responsive items to conduct an initial Rasch analysis. Of those 3 lists, 1 represented use of products and technology, 1

represented the natural environment and man-made changes to the environment, and 1 represented support and relationships. None of the domains demonstrated acceptable person-separation indices.

Table V.4: Psychometric / Rasch analysis summary statistics for responsive item lists by domain/subdomain

Psychometric / Rasch Analysis Summary Statistics for Responsive Item Lists by Domain/Subdomain							
Domain/Subdomain	CFA # of Factors	Cronbach's Alpha	Item Fit Residual (mean[SD])	Person Fit Residual (mean[SD])	PSI (w/Extremes)	PSI (w/o Extremes)	Person/Item Separation Index
ICF Part B: Function							
Subdomain: Mental Function							
Intellectual Function	ND	ND	ND	ND	ND	ND	ND
Temperament and Personality Functions	ND	ND	ND	ND	ND	ND	ND
Energy and Drive Functions	ND	ND	ND	ND	ND	ND	ND
Sleep Functions	1	0.531	-4.6(2.7)	-0.32(0.76)	0.197	-0.332	0.278
Attention Functions	ND	ND	ND	ND	ND	ND	ND
Memory Functions	ND	ND	ND	ND	ND	ND	ND
Emotional Functions: Anxiety	ND	ND	ND	ND	ND	ND	ND
Emotional Functions: Depression	ND	ND	ND	ND	ND	ND	ND
Emotional Functions: Fear	ND	ND	ND	ND	ND	ND	ND
Emotional Functions: Frustration	ND	ND	ND	ND	ND	ND	ND
Emotional Functions: Satisfaction	ND	ND	ND	ND	ND	ND	ND
Subdomain: Sensory Functions and Pain							
Sensory Functions and Pain	1	0.51 - 0.776	-3.6(2.7)	-0.71(0.82)	0.329	0.064	0.074
Subdomain: Functions of the Cardiovascular, Hematological, Immunological and Respiratory Systems							
Functions of the Hematological and Immunological Systems	ND	ND	ND	ND	ND	ND	ND
Functions of the Respiratory System	ND	ND	ND	ND	ND	ND	ND
Functons Related to the Digestive System	ND	ND	ND	ND	ND	ND	ND
Functions Related to Metabolism and the Endocrine System	ND	ND	ND	ND	ND	ND	ND
Subdomain: Neuromusculoskeletal and Movement-Related Functions							
PUL High Level: Shoulder Dimension	2	0.891	0.51(8.19)	-0.28(1.08)	0.793	0.761	0.767
PUL Mid-Level: Elbow Dimension	3	0.952	0.18(1.59)	-0.33(0.68)	0.713	0.583	0.586
PUL Distal-Level: Wrist and Finger Dimension	5	0.763	0.26(3.70)	-0.94(0.64)	-0.646	-0.472	-0.44
Complex: Standing from Supine	ND	0.949	0.73(0.61)	0.21(0.25)	0.760	0.790	0.859
Complex: Standing from Seated	3	0.755	-0.2(2.14)	-0.42(0.51)	-0.111	-3.972	-3.293
Complex: Transfers	3	0.970	0.48(2.8)	-0.71(0.91)	0.035	-2.230	-1.997
Head/Neck	ND	ND	ND	ND	ND	ND	ND
Trunk: Standing	4	0.935	1.04(1.35)	-0.30(1.28)	0.034	-0.685	-0.587
Trunk: Sitting	5	0.957	-0.97(2.56)	-0.37(0.71)	0.717	0.616	0.619
LL: Running	3	0.596	0.36(5.04)	-0.34(1.34)	0.490	0.578	0.581
LL: Climbing	2	0.953	-0.02(4.31)	-0.39(0.79)	0.772	0.689	0.691
LL: Walking	5	0.966	-0.93(5.46)	-0.30(1.21)	0.756	0.782	0.786
Subdomain: Functions of the Skin and Related Structures							
Functions of the Skin and Related Structures	ND	ND	ND	ND	ND	ND	ND
ICF Part D: Activities and Participation							
Subdomain: Learning and Applying Knowledge							
Learning and Applying Knowledge	1	0.691	-0.04(2.39)	-0.44(0.78)	0.561	0.415	0.421
Subdomain: General Tasks and Demands							
Undertaking Multiple Tasks	ND	ND	ND	ND	ND	ND	ND
Carrying Out a Daily Routine	ND	ND	ND	ND	ND	ND	ND
Handling Stress and Other Psychological Demands	ND	ND	ND	ND	ND	ND	ND
Subdomain: Communication							
Communication	3	0.125	0.02(3.58)	-0.40(0.26)	-1.068	-3.034	-2.93
Subdomain: Mobility							
Changing and Maintaining Body Position	3	0.986	-1.00(4.06)	-0.38(1.02)	0.848	0.848	0.850
Carrying, Moving and Handling Objects	3	0.956	0.42(5.22)	-0.29(1.11)	0.735	0.701	0.704
Walking and Moving	ND (highly collinear)	0.929	-1.65(6.70)	-0.58(1.28)	-0.312	0.885	0.887
Moving Around Using Transportation	ND	ND	ND	ND	ND	ND	ND
Subdomain: Self-Care							
Washing Onesself	3	0.553	0.45(2.41)	-1.13(1.31)	-1.192	-2.535	-2.117
Caring for Body Parts	1	0.921	0.13(2.26)	-0.22(0.18)	-0.163	-3.068	-2.960
Toileting	2	0.915	-0.42(1.40)	-1.28(1.06)	0.558	0.234	0.277
Dressing	2	0.961	0.82(1.14)	-0.44(0.93)	0.535	-0.026	-0.009
Eating	ND	0.838	0.73(0.28)	-0.13(0.13)	-0.272	-1.99	-1.760
Drinking	ND	ND	ND	ND	ND	ND	ND
Looking After One's Health	ND	0.531	-0.38(2.35)	-0.28(0.73)	0.198	-0.333	-0.289
Subdomain: Domestic Life							
Domestic Life	ND	ND	ND	ND	ND	ND	ND
Subdomain: Interpersonal Interactions and Relationships							
Informal Social Relationships	ND	ND	ND	ND	ND	ND	ND
Family Relationships	ND	0.723	0.67(0.49)	-0.45(0.93)	0.359	0.305	0.345
Intimate Relationships	ND	ND	ND	ND	ND	ND	ND
Subdomain: Major Life Areas							
Major Life Areas	ND	ND	ND	ND	ND	ND	ND
Subdomain: Community, Social and Civic Life							
Community Life	ND	ND	ND	ND	ND	ND	ND
Recreation and Leisure	3	0.804	0.81(4.60)	-0.30(1.17)	0.501	0.448	0.454
ICF Part E: Environmental Factors							
Subdomain: Products and Technology							
Products and Technology	ND (highly collinear)	0.268	-0.06(3.55)	-0.60(1.13)	0.276	0.390	0.445
Subdomain: Natural Environment and Human-Made Changes to the Environment							
Natural Environment and Human-Made Changes to Environment	1	0.866	-0.05(0.64)	-0.22(0.37)	0.697	0.576	0.600
Subdomain: Support and Relationships							
Support and Relationships	1	0.799	0.36(1.31)	-0.45(1.19)	0.554	0.544	0.57
Subdomain: Attitudes							
Attitudes	ND	ND	ND	ND	ND	ND	ND
Subdomain: Services, Systems and Policies							
Services, Systems and Policies	ND	ND	ND	ND	ND	ND	ND

** Note: A total of n=366 question items were reviewed. Each question was assigned to subdomains in Part B, Part D and Part E as applicable.*

*** ND = Not done due to having too few or no items unless otherwise noted.*

Construct and Item Selection

Based on the first-pass Rasch analysis results, we selected the ICF Part D Activities and Participation Mobility domain question lists for further study and refinement using a second pass Rasch analysis. Selection of these subdomains, representing Walking and Moving, Changing and Maintaining Body Position, and Carrying, Moving and Handling Objects was not entirely unexpected because the initial responsive item evaluation was based on the concept of item change over time and with progressive loss of strength. In addition, the overall Activities and Participation Mobility construct represents multiple mobility functions across functional groups, where the Structure and Function neuromusculoskeletal and movement-related function-based lists focused tasks on specific affected parts of the body, thus limiting question set applicability to subpopulations where that function is still possible. The resulting questions comprise three domain-based item lists (Tables V.5 – V.7) reflecting a general latent construct of mobility, including functions of the upper extremities, trunk stability and lower extremities using person-reported question items representing

crucial functions across the lifespan from early childhood to adulthood. The item lists included questions from the POSNA PODCI, PedsQL, PedsQL Neuromuscular Module and Neuro-QoL instruments. These items are questions with polytomous 1-4 or 1-5 Likert-type response ratings representing level of difficulty of performing a specific task (eg. climbing stairs).

Principle component analysis of the 3 item lists demonstrated multidimensionality in two. In the Changing and Maintaining Body Position question list, 3 factors suggested underlying functions associated with transfers and positional changes (Factor 1), standing from seated or supine (Factor 2), and unsupported sitting (Factor 3). In the Carrying, Moving and Handling Objects list, 3 factors suggested underlying functions associated with tasks that require strength (Factor 1), tasks that require manual dexterity (Factor 2), and a factor that may suggest manual tasks done in a wheelchair (Factor 3). Taken together the questions represent a range of function from near full function to significant impairment lacking the ability to walk and with minimal use of hands and reduced respiratory capacity.

Table V.5: Disease Progression-Responsive Item List for Walking and Moving

Instrument	Item Number / Question
NeuroQOL	1. I could keep my balance while walking for 30 minutes
NeuroQOL	4. I could walk for 15 minutes
NeuroQOL	5. I could walk between rooms
NeuroQOL	12. I could walk for 30 minutes
NeuroQOL	20. I fall down easily
NeuroQOL	21. I could walk on slightly uneven surfaces (such as cracked pavement)
NeuroQOL	22. I lose my balance easily
NeuroQOL	24. I could walk on rough, uneven surfaces (such as lawns, gravel driveway)
NeuroQOL	25. I could walk up and down ramps or hills
NeuroQOL	26. I could walk up and down curbs
NeuroQOL	31. I could walk across the room.
NeuroQOL	39. I could walk up 2-3 stairs
PedsQL	1. Walking more than one block
PedsQL	2. Running
POSNA PODCI	38. Run short distances?
POSNA PODCI	39. Bicycle or tricycle?
POSNA PODCI	40. Climb three flights of stairs?
POSNA PODCI	42. Walk more than a mile?
POSNA PODCI	43. Walk three blocks?
POSNA PODCI	44. Walk one block?
POSNA PODCI	34. How often does your child need help from another person for walking and cliimbing?
POSNA PODCI	52. How often did your child need help from another person for propelling a wheelchair outside on uneven surfaces such as grass, sidewalk or gravel?
POSNA PODCI	54. During the past one month, has it been easy or hard for your child to drive his power wheelchair or scooter by himself?

Table V.6: Disease Progression-Responsive Item List for Changing and Maintaining Body Position

Instrument	Item Number / Question
Factor 1: Transfers and Positional Changes	
NeuroQOL	4. I could move between my wheelchair and another seat such as a chair or bed
NeuroQOL	6. I could manage getting on and off the tub bench from a wheelchair
NeuroQOL	7. I could manage getting on and off the toilet from a wheelchair
NeuroQOL	10. I could get in and out of an adultsized chair
PedsQL NMM	16. It is hard to turn myself during the night.
NeuroQOL	16. I could keep my balance while walking for 15 minutes

NeuroQOL	19. I could turn my head all the way to the side to look at someone or something
NeuroQOL	21. I was able to cover my nose when sneezing
NeuroQOL	26. I was able to change positions in my bed.
POSNA PODCI	33. How often did your child use assistive devices (such as braces, crutches or a wheelchair) for walking or climbing?
POSNA PODCI	25. Stand while washing his hands and face at a sink?
POSNA PODCI	26. Sit in a regular chair without holding on?
POSNA PODCI	27. Get on and off a toilet or chair?
NeuroQOL	30. I was able to get out of bed by myself.
POSNA PODCI	28. Get in and out of bed?
NeuroQOL	31. I was able to get into bed by myself.
POSNA PODCI	31. How often did your child need help from another person for sitting and standing?
POSNA PODCI	32. How often did your child use assistive devices (such as braces, crutches or a wheelchair) for sitting and standing?
Factor 2: Standing from Seated or Supine	
NeuroQOL	2. I could get down on my knees without holding on to something.
NeuroQOL	8. I could stand up from an armless straight chair using my wheelchair
NeuroQOL	9. I could get on and off a low chair
NeuroQOL	11. I could get on and off a chair without using my arms.
NeuroQOL	13. I could get up from the floor by myself
NeuroQOL	17. I could stand on my tiptoes to reach for something
POSNA PODCI	30. Bend over from a standing position and pick up something off the floor?
NeuroQOL	33. I could bend over to pick something up.
Factor 3: Unsupported Sitting	
NeuroQOL	14. I could sit on a bench without support for 15 minutes
NeuroQOL	15. I could sit on a bench without back support for 30 minutes

Table V.7: Disease Progression-Responsive Item List for Carrying, Moving and Handling Objects

Instrument	**Item Number / Question**
Factor 1: Tasks that require strength	
POSNA PODCI	7. Lift heavy books?
POSNA PODCI	8. Pour a half gallon of milk?
POSNA PODCI	9. Open a jar that's been opened before?
PedsQL	4. Lifting something heavy
NeuroQOL	17. I was able to pick up a gallon of milk with one hand and set it on the table
NeuroQOL	33. I was able to open a jar by myself.
NeuroQOL	36. I was able to pull open heavy doors.
NeuroQOL	37. I was able to open the rings in school binders.
Factor 2: Tasks that require manual dexterity	
NeuroQOL	1. I was able to open small containers like snack bags or vitamins (regular screw top)
NeuroQOL	8. I was able to hold a full cup of water in my hand.
PedsQL NMM	8. My hands are weak.
PedsQL NMM	11. It is hard to use my hands.
NeuroQOL	12. I was able to use a knife to spread butter or jelly on bread
NeuroQOL	15. I was able to hold a plate full of food
NeuroQOL	19. I was able to cut a piece of paper in half with scissors

NeuroQOL	23. I was able to open a can of soda
POSNA PODCI	29. Turn doorknobs?
Factor 3: Manual tasks from a wheelchair.	
NeuroQOL	16. I could open a door that faced away from my wheelchair
NeuroQOL	17. I could open a door that was facing my wheelchair
NeuroQOL	19. I could manage the armrests on my wheelchair
NeuroQOL	20. I could manage the footrests on my wheelchair.

Rasch Analysis of the Activities and Participation Mobility Domain and Subdomains.

Walking and Moving
First Pass Analysis

In the first pass Rasch analysis, a person separation index of 0.88 demonstrated an excellent power of the overall model to individuate between respondents. Summary statistics showed that using all response items to model a "latent" construct of walking and moving ability across ambulatory and non-ambulatory stages of disease moderately over-discriminated, with a fit residual mean(SD) of -1.65(6.7), and a person fit residual mean(SD) of -0.58(1.28). The negative mean fit residual suggested that there was some degree of response dependency between items that required exploration. Review of individual item fit characteristics suggested that of the 23 items included in the model, 14 either contributed appreciably to model misfit (with an item residual >|3.0|), or showed non-random patterns in their variance (chi square p-values <0.01). Seven of the 23 items demonstrated ordered response thresholds. Results of first pass analyses are shown in detail in Appendix V.1 (ICF Domain Construct Question List and Analyses).

Item Rescoring: The first pass analysis revealed multiple items with disordered item response thresholds, indicating a lack of uniformity in the way individuals select question response choices, such as choices "with a little trouble" and "with some trouble", or "never" and "almost never", or "almost never" and "sometimes". For items such as these with overlapping response curves, we rescored the items to combine overlapping responses into a single score. Eighteen items were rescored. Following rescoring, items displayed ordered response thresholds, but also demonstrated high residuals indicating poor overall model fit. As a result, nine items were dropped, resulting in a final list of 15 items representing ambulatory functions. Changes to the question list and the response scoring structure are indicated in in Appendix V.1 (ICF Domain Construct Question List and Analyses).

Second-Pass Analysis

Model and Item Fit: Because the remaining questions all addressed ambulatory ability, analysis was restricted to individuals with ambulatory milestone scores only, and included 1,498 scorable responses and 139 extreme scores. In the second pass analysis, the person separation index at 0.88 continued to demonstrate very good power of the overall model to individuate between respondents. Summary statistics showed that using the selected subset of response items to model a construct of ambulatory ability still moderately over-discriminated, with a fit residual mean(SD) of -0.55(2.39), and a person fit residual mean(SD) of -0.36(0.98). The negative fit residual suggests that there is still a degree of response dependency that requires exploration. Fit statistics for the final model are displayed in Table V.8. Review of individual item fit (Table V.9) suggested that of the 15 items included in the model, 3 continue to contribute somewhat to model misfit (with an item residual >|3.0|).

Table V.8. Summary Test of Fit Statistics

Item Fit	**Fit Residual Mean**	**SD**
	-0.55	2.39
Person Fit	-0.36	0.98
Chi Squared Probability	1.0000	
Degrees of freedom	132	
Person Separation Index (PSI)	0.88	

Table V.9. Individual Item Fit for the 15 Items by item location (i.e. order of difficulty, most difficult to easiest). Items contributing to model Mis-fit items are shown in BOLD.

Seq	Item	Type	Location	SE	Residual	DF	ChiSq	DF	Prob	F-stat	DF1	DF2	Prob
5	Q5	Poly	-3.654	0.513	-0.158	38.43	1.758	8	0.987543	...	...	...	...
13	Q13	Poly	-1.342	0.256	-0.512	38.43	0.790	8	0.999258	...	...	...	...
18	Q18	Poly	-1.100	0.252	-0.423	38.43	0.429	8	0.999926	...	...	...	...
17	**Q17**	**Poly**	**-1.065**	**0.047**	**-4.010**	**1236.51**	**7.130**	**9**	**0.623609**	...	...	...	...
1	Q1	Poly	-0.675	0.296	0.070	37.60	1.377	9	0.997960	...	...	...	...
20	Q20	Poly	-0.114	0.306	0.465	37.60	1.364	9	0.998034	...	...	...	...
12	Q12	Poly	0.096	0.045	-2.884	1238.18	5.103	9	0.825255	...	...	...	...
23	Q23	Poly	0.164	0.303	-1.136	36.76	1.450	9	0.997499	...	...	...	...
4	Q4	Poly	0.208	0.301	-0.233	37.60	0.945	9	0.999554	...	...	...	...
19	Q19	Poly	0.507	0.328	0.319	37.60	1.997	9	0.991515	...	...	...	...
7	**Q7**	**Poly**	**0.755**	**0.052**	**5.978**	**1247.37**	**6.757**	**9**	**0.662455**	...	...	...	...
16	**Q16**	**Poly**	**0.765**	**0.043**	**-4.618**	**1236.51**	**7.083**	**9**	**0.628463**	...	...	...	...
6	Q6	Poly	1.522	0.338	-0.791	37.60	1.435	9	0.997598	...	...	...	...
9	Q9	Poly	1.837	0.046	-0.715	1243.19	2.725	9	0.974214	...	...	...	...
14	Q14	Poly	2.096	0.045	0.390	1243.19	3.516	9	0.940286	...	...	...	...

Individual Person Fit: Residuals values for person fit represent the difference between modelled responses and the individual's actual responses. Residual fit values < |3.0| can be considered acceptable. Residuals for individual person fit ranged from -4.18 to 2.56 (mean -0.36, SD 0.98) indicating that overall, individuals in the sample fit the model well, with only 1 response (0.07%) falling outside the acceptable range.

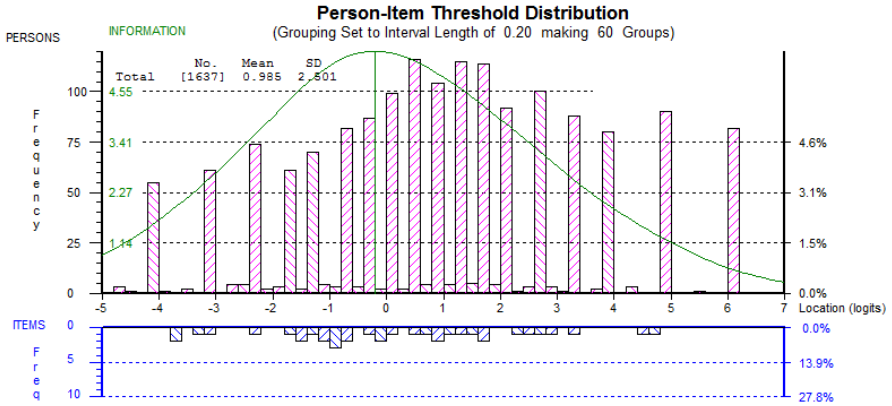
Correlation of Residuals: Items in this domain-based list represent a latent construct of mobility in the context of a progressively debilitating disease measured using different representations (ie. standing, climbing, walking, breathing) of that mobility or lack thereof. Thus, we expect a moderate degree of covariation or dependency between variables, where a response on two items (ex. Ability to walk 1 block vs. Ability to walk 3 blocks) are both dependent on the underlying ability to walk long distances. For purposes of this analysis, we were willing to accept a moderate degree of correlation (ie. <0.4) between items. Items exceeding our acceptable limit of moderate residual correlation are shown in **Table V.10**. Of the items with moderately correlated residuals, only Question 13 and Question 18 seem to represent a similar function of walking on uneven surfaces. The remainder of the correlated items seem to represent items that are expected go together at different levels of function, most specifically items oriented toward walking distances versus climbing grades. Thus, we have selected to include these items in the model. It may be possible at some later point to condense these items into one or more questions with responses that capture a continuum of function, thus reducing or eliminating local dependency.

Table V.10. Local Dependency for Walking and Moving Scale Items

	Q1	Q4	Q9	Q12	Q13	Q16	Q17	Q18
Q12	-0.474	-0.499						
Q16	-0.417		-0.413	-0.458				
Q17					-0.781			
Q18					0.434	-0.400	-0.647	
Q19				-0.583				
Q20						-0.469	-0.495	
Q23					0.418	-0.524	-0.707	0.481

Person-Item Threshold Location: The person-item threshold distribution shown in **Figure V.3** reflects the overall distribution of the population examined (persons in pink), in this case children and adolescents with Duchenne muscular dystrophy, over a continuous logit scale. The individuals' position on the scale represents their overall level of function in a latent construct representation of ambulatory mobility as assessed using the selected set of person-reported response items from our Duchenne natural history study. The blue items then indicate the position of item thresholds, or points of change, between response categories for items included in the mobility domain list, and represent boundaries of the domain list's ability to readily differentiate between individuals at a given level of function. Points to the left indicate better function, points to the right indicate worse function. The distribution indictates that approximately 10% of respondents score to the right of the measurable scale (ie. ceiling effect), and slightly over 3% score to the left (ie. floor effect). This suggests that the current list does an acceptable job of assessing differences across a range of ambulatory individuals who are mildly affected to those who are on the verge of losing ambulation, but that it may lack the ability to evaluate individuals who are more severely affected. When evaluated by age group, mean(SD) scores for <4, 4-6, 7-9, 10-12, 13-15, 16-18 year old participants are statistically significantly different (p=0.0000001) at 2.1(1.26), 1.96(2.12), 1.43(2.35), 0.19(2.54), 0.21(2.63) and -0.65(1.75) respectively, in a pattern that overlaps but that is consistent with our understanding of disease progression with age in DMD. However, when evaluated according to clinically-measured functional milestones, those differences become more pronounced between individuals who are fully functional (Group 0), those who have lost the ability to stand from supine (Group 1), those who have in addition lost the ability to climb stairs (Group 2), and those who have subsequently lost the ability to rise from a chair but who remain ambulatory (Group 3). Group mean(SD) scores for those grades are statistically significantly different (p=0.0000001) at 1.65(2.27), -0.36(2.04), -1.84(1.67) and -2.35(1.56), respectively.

Figure V.3. Person-Item Threshold Distribution for the Walking and Moving Question Set

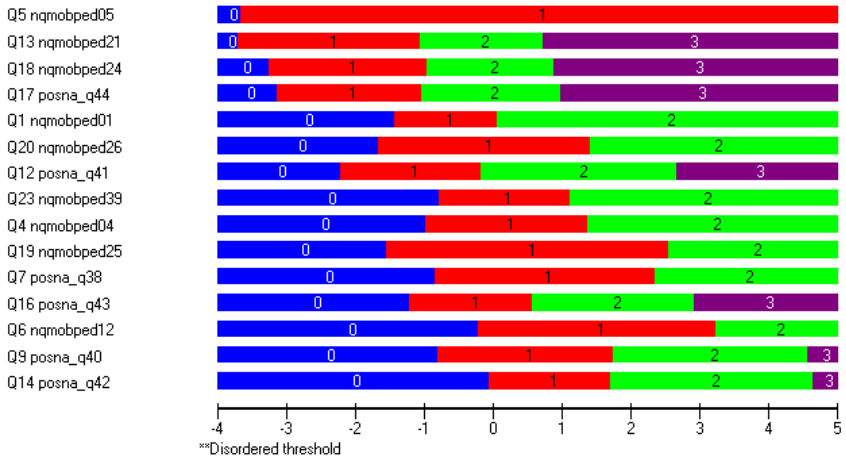


Threshold Ordering, Item Locations and Clinical "Face" Validity: Placing the questions in location order from easiest to most difficult yields the draft question set noted in **Table V.11**. The item location threshold map is presented as **Figure V.4**. Overall, these items represent a range of ambulatory mobility tasks that are progressively lost, starting with long distance and long duration walks and climbs, and running, followed by moderate distance and duration walks and climbs, followed by short walks, walks on uneven surfaces, and walking household distances. This is consistent with the clinical presentation and natural history of the disease and spans nearly the entire range of ambulatory function, suggesting that our construct has face validity as a representation of mobility.

Table V.11: Final Draft Walking and Moving Question Set

Q5	nqmobped05	I could walk between rooms
Q13	nqmobped21	I could walk on slightly uneven surfaces (such as cracked pavement)
Q18	nqmobped24	I could walk on rough, uneven surfaces (such as lawns, gravel driveway)
Q17	posna_q44	Walk one block?
Q1	nqmobped01	I could keep my balance while walking for 30 minutes
Q20	nqmobped26	I could walk up and down curbs
Q12	posna_q41	Climb one flight of stairs?
Q23	nqmobped39	I could walk up 2-3 stairs
Q4	nqmobped04	I could walk for 15 minutes
Q19	nqmobped25	I could walk up and down ramps or hills
Q7	posna_q38	Run short distances?
Q16	posna_q43	Walk three blocks?
Q6	nqmobped12	I could walk for 30 minutes
Q9	posna_q40	Climb three flights of stairs?
Q14	posna_q42	Walk more than a mile?

Figure V.4: Draft Walking and Moving Question Set Item Location Threshold Map.



Changing and Maintaining Body Position

First Pass Analysis

In the first pass analysis, a person separation index of 0.84 demonstrated an excellent power of the overall model to individuate between respondents. Summary statistics showed that using all response items to model a "latent" construct of trunk stability across ambulatory and non-ambulatory stages of disease moderately over-discriminated, with a fit residual mean(SD) of -1.00(4.06) and a person fit residual mean(SD) of -0.38(1.02). The negative mean fit residual suggested that there was some degree of response dependency between items that required exploration. Review of individual item fit characteristics suggested that of the 28 items included in the model, 9 either contributed appreciably to model fit or showed non-random patterns in their variance. Twelve of the 28 items demonstrated ordered response thresholds. Results of first pass analyses are shown in detail in Appendix V.1 (ICF Domain Construct Question List and Analyses).

Item Rescoring: The first pass analysis revealed multiple items with disordered item response thresholds, indicating a lack of uniformity in the way individuals select question response choices, such as choices "with a little trouble" and "with some trouble", or "never" and "almost never", or "almost never" and "sometimes". For items such as these with overlapping response curves, we rescored the items to combine overlapping responses into a single score. Sixteen items were rescored. Following rescoring, items displayed ordered response thresholds. All items were retained in the model, resulting in a final list of 28 items representing functions related to changing and maintaining body position. Changes to the response scoring structure are indicated in in Appendix V.1 (ICF Domain Construct Question List and Analyses).

Second Pass Analysis

Model and Item Fit: The questions presented in the list represent a range of functions that do not directly require the ability to ambulate, and thus the analysis included responses from all participants. Available data included 2,324 scorable responses and 927 extreme scores. In the second pass analysis, the person separation index at 0.86 continued to demonstrate very good power of the overall model to individuate between respondents. Summary statistics showed that using the selected subset of response items to model a construct of representing mobility during positional transfers still moderately over-discriminated, with a fit residual mean(SD) of -1.02(4.05), and a person fit residual mean(SD) of -0.45(1.29). The negative fit residual suggests that there is still a degree of response dependency that requires exploration. Fit statistics for the final model are displayed in Table V.12. Review of individual item fit (Table V.13) suggested that of the 28 items included in the model, 6 continue to contribute somewhat to model misfit (with an item residual >|3.0|).

Table V.12. Summary Test of Fit Statistics

Item Fit	**Fit Residual Mean**	**SD**
	-1.42	4.05
Person Fit	-0.45	1.29
Chi Squared Probability	0.999992	
Degrees of freedom	251	

Person Separation Index (PSI)	0.86	

Table V.13. Individual Item Fit for the 28 items. Items contributing to model mis-fit items are shown in BOLD.

Seq	Item	Type	Location	SE	FitResid	DF	ChiSq	DF	Prob		
1	Q1	Poly	2.512		0.234	-1.069		82.03	0.644	9	0.999911
2	Q2	Poly	-0.601		0.175	2.309		72.32	3.437	9	0.944436
3	Q3	Poly	0.054		0.187	1.349		67.03	1.551	8	0.991836
4	Q4	Poly	-0.333		0.236	-1.836		68.80	1.473	9	0.997344
5	Q5	Poly	-0.113		0.231	0.672		68.80	0.950	9	0.999544
6	Q6	Poly	1.332		0.247	-1.411		82.91	0.803	9	0.999773
7	Q7	Poly	0.180		0.228	-1.174		82.03	1.379	9	0.997949
8	Q8	Poly	2.517		0.280	-0.980		82.91	0.781	9	0.999798
9	Q9	Poly	2.228		0.279	-0.518		82.03	1.117	9	0.999117
10	Q10	Poly	-0.903		0.171	1.668		85.55	2.434	9	0.982607
11	Q11	Poly	0.304		0.172	2.158		85.55	10.129	9	0.340126
12	Q12	Poly	-1.354		0.142	-1.130		239.02	1.090	9	0.999201
13	Q13	Poly	0.653		0.227	-1.795		82.03	0.940	9	0.999563
14	Q14	Poly	1.436		0.199	-1.238		82.03	1.096	9	0.999182
15	Q15	Poly	-3.518		0.169	0.022		88.20	1.543	9	0.996812
16	Q16	Poly	-3.047		0.207	-0.207		94.37	0.359	9	0.999993
17	Q17	Poly	-1.044		0.169	1.134		88.20	1.495	9	0.997186
18	**Q18**	**Poly**	**-0.194**		**0.040**	**8.776**		**1991.56**	**13.183**	**9**	**0.154485**
19	**Q19**	**Poly**	**-0.379**		**0.040**	**-8.788**		**2003.03**	**17.583**	**9**	**0.040329**
20	**Q20**	**Poly**	**-1.840**		**0.043**	**4.278**		**2028.60**	**37.566**	**9**	**0.000021**
21	**Q21**	**Poly**	**0.266**		**0.041**	**-10.759**		**2021.55**	**21.876**	**9**	**0.009280**
22	Q22	Poly	-0.304		0.171	-2.460		87.32	0.858	9	0.999702
23	**Q23**	**Poly**	**-0.175**		**0.041**	**-10.698**		**2022.43**	**22.708**	**9**	**0.006887**
24	Q24	Poly	-0.290		0.170	-2.313		85.55	0.906	9	0.999626
25	**Q25**	**Poly**	**1.380**		**0.035**	**-5.266**		**2011.85**	**6.512**	**9**	**0.687816**
26	Q26	Poly	1.522		0.206	-0.002		82.03	1.131	9	0.999071
27	Q27	Poly	0.168		0.041	0.297		2000.38	7.519	9	0.583239
28	Q28	Poly	-0.458		0.040	0.301		2003.91	4.464	9	0.878324

Individual Person Fit: Residuals values for person fit represent the difference between modelled responses and the individual's actual responses. Residual fit values < |3.0| can be considered acceptable. Residuals for individual person fit ranged from -22.6 to 3.08 (mean -0.45, SD 1.29) indicating that overall, individuals in the sample fit the model moderately well, with 43 responses (1.8%) falling outside the acceptable range.

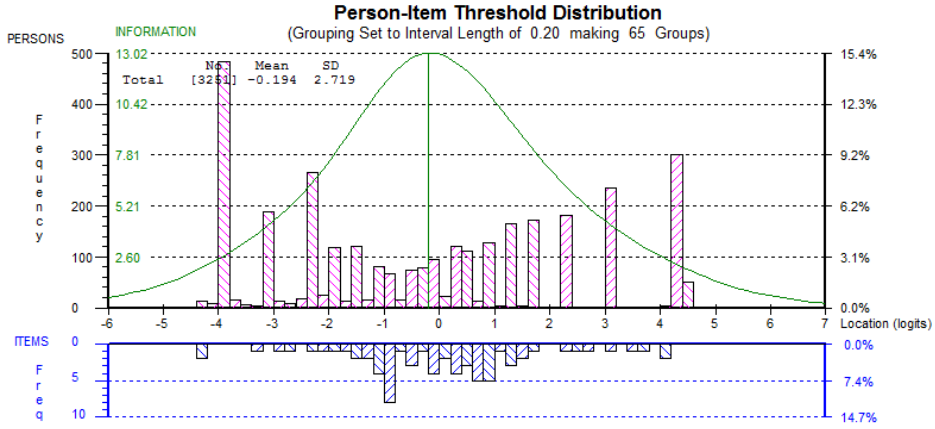
Correlation of Residuals: As noted previously, for purposes of this analysis we were willing to accept a moderate degree of correlation (ie. <0.4) between items. Items exceeding our acceptable limit of moderate residual correlation are shown in **Table V.14**. Q1 is getting down on knees without holding on to something. This correlates moderately with getting out of chairs, getting up from the floor, and use of assistive devices. Q4 is getting on/off a toilet from a wheelchair, which correlates with Q11 sitting on a bench without back support for >30 minutes. Q10 is sitting on a bench for >15 minutes, which correlates with sitting on a bench for >30 minutes, and getting out of bed. Q19 is standing at a sink, which correlates with getting into bed. Q22 is getting out if bed, which correlates with Q24 getting into bed, and Q23 getting into and out of bed. In similar fashion, Q23 and Q24 are correlated. Q24 getting into bed also correlates moderately with bending over to pick something up. It is clear that many of these items constitute questions regarding similar functions. However, the similar function items are often from different instruments (ie. PODCI versus NeuroQoL) which were not uniformly administered across the participant age groups, because NeuroQoL items were added to a more recent version of the protocol. Thus, dropping one item in favour of the other results in significant reduction in the overall sample available for analysis. Thus, we have elected to include these items in the model. However, it will be necessary during further instrument validation to condense these items into one or more questions that can be uniformly administered to future study populations.

Table V.14. Local Dependency for Changing and Maintaining Body Position Scale Items

	Q1	Q4	Q10	Q19	Q22	Q23	Q24
Q6	0.560						
Q8	0.412						
Q9	0.443						
Q11		0.416	0.492				
Q18	-0.471						
Q22			-0.431				
Q23					0.460		
Q24				0.519	0.780	0.451	
Q26							-0.42
Q28	-0.457						

Person-Item Threshold Location: The person-item threshold distribution shown in **Figure V.5** reflects the overall distribution of the population examined (persons in pink), in this case individuals with Duchenne muscular dystrophy, over a continuous logit scale. The distribution indictates that approximately 12% of respondents score to the right of the measurable scale (ie. ceiling effect), and slightly over 18% score to the left (ie. floor effect). This suggests that the current list does an acceptable job of assessing differences across a range of ambulatory and non-ambulatory individuals from those who are ambulatory and moderately affected to those who have lost ambulation but still retain some ability to sit unsupported. When evaluated by age group, mean(SD) scores for <4, 4-6, 7-9, 10-12, 13-15, and 16-18 year old participants are statistically significantly different (p=0.0000001) at 3.6(1.32), 2.76(1.43), 1.98(1.91), -0.54(2.47), -1.56(2.27) and -2.17(1.83) respectively, in a pattern that overlaps but that is consistent with our understanding of disease progression with age in DMD. When evaluated according to clinically-measured functional milestones across the entire disease severity spectrum, those differences remain pronounced between individuals who are fully functional (Group 0), those who have lost the ability to stand from supine (Group 1), those who have in addition lost the ability to climb stairs (Group 2), those who have subsequently lost the ability to rise from a chair but who remain ambulatory (Group 3), those who have lost the ability to walk but who can bring their hand to their mouth (Group 4), those who have lost the ability to bring their hand to their mouth (Group 5), and those who cannot bring their hand to their mouth and have a forced vital capacity <30% predicted (Group 6). Group mean(SD) scores for those groups are statistically significantly different (p=0.0000001) at 2.52(1.49), 1.01(1.21), 0.25(0.84), -0.49(0.85), -2.28(1.30), -2.92(1.17) and -3.01(1.16), respectively.

Figure V.5. Person-Item Threshold Distribution for the Changing and Maintaining Body Position Question Set



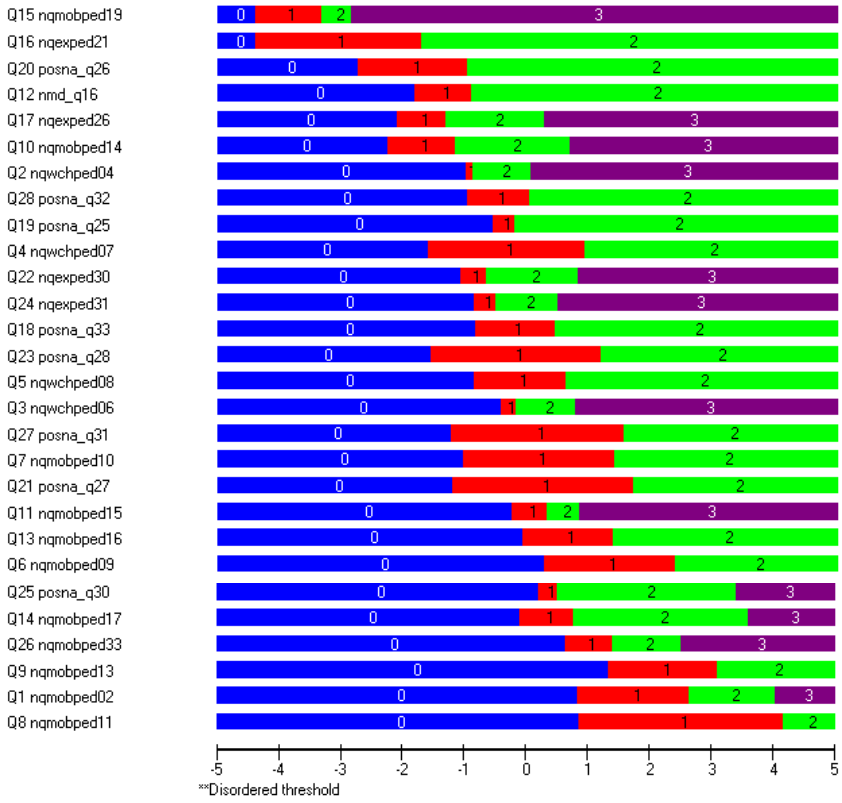
Threshold Ordering, Item Locations and Clinical "Face" Validity: Placing the questions in location order from easiest to most difficult yields the draft question set noted in **Table V.15**. The item location threshold map is presented as **Figure V.6**. Overall, these items represent a range of positional change and transfer abilities that are progressively lost, starting with standing from a chair without use of the arms, followed by bending to pick items off of the floor, followed by self-transfer to a chair, toilet or bed using the arms, followed by changing positions in bed, followed by ability to turn the head. This is consistent with the clinical presentation and natural history of the disease and spans a large range of function, suggesting that our construct has face validity as a representation of transfer and positional change mobility. Referring to the apparent latent factors identified in the principle component analysis, items aligning with the second factor (standing from seated or supine) predominate in the stronger end of the spectrum, while items aligning

with the first factor (transfers and positional changes) predominate in the weaker 2/3 of the scale. Tasks associated with the third factor (unsupported sitting) end up in the middle and probably represent a short period of time where individuals are wheelchair users but still have some ability to maintain seated balance and trunk posture. As discussed previously, several of these questions from different instruments used in different sub-populations duplicate similar activities and align in similar fashion with respect to order of difficulty. Those questions could be condensed into single items and re-tested.

Table V.15: Final Draft Changing and Maintaining Body Position Question Set

Q15	nqmobped19	I could turn my head all the way to the side to look at someone or something
Q16	nqexped21	I was able to cover my nose when sneezing
Q20	posna_q26	Sit in a regular chair without holding on?
Q12	nmd_q16	It is hard to turn myself during the night.
Q17	nqexped26	I was able to change positions in my bed
Q10	nqmobped14	I could sit on a bench without support for 15 minutes
Q2	nqwchped04	I could move between my wheelchair and another seat such as a chair or bed
Q28	posna_q32	How often did your child use assistive devices (such as braces, crutches or a wheelchair) for sitting and standing?
Q19	posna_q25	Stand while washing his hands and face at a sink?
Q4	nqwchped07	I could manage getting on and off the toilet from a wheelchair
Q22	nqexped30	I was able to get out of bed by myself.
Q24	nqexped31	I was able to get into bed by myself.
Q18	posna_q33	How often did your child use assistive devices (such as braces, crutches or a wheelchair) for walking or climbing?
Q23	posna_q28	Get in and out of bed?
Q5	nqwchped08	I could stand up from an armless straight chair using my wheelchair
Q3	nqwchped06	I could manage getting on and off the tub bench from a wheelchair
Q27	posna_q31	How often did your child need help from another person for sitting and standing?
Q7	nqmobped10	I could get in and out of an adultsized chair
Q21	posna_q27	Get on and off a toilet or chair?
Q11	nqmobped15	I could sit on a bench without back support for 30 minutes
Q13	nqmobped16	I could keep my balance while walking for 15 minutes
Q6	nqmobped09	I could get on and off a low chair
Q25	posna_q30	Bend over from a standing position and pick up something off the floor?
Q14	nqmobped17	I could stand on my tiptoes to reach for something
Q26	nqmobped33	I could bend over to pick something up.
Q9	nqmobped13	I could get up from the floor by myself
Q1	nqmobped02	I could get down on my knees without holding on to something.
Q8	nqmobped11	I could get on and off a chair without using my arms.

Figure V.6: Draft Changing and Maintaining Body Position Question Set Item Location Threshold Map.



Carrying, Moving and Handling Objects

First Pass Analysis

In the first pass analysis, a person separation index of 0.73 demonstrated acceptable power of the overall model to individuate between respondents. Summary statistics showed that using all response items to model a "latent" construct of upper extremity ability across ambulatory and non-ambulatory stages of disease discriminates moderately well, with a fit residual mean(SD) of 0.42(5.21) and a person fit residual mean(SD) of -0.29(1.10). Review of individual item fit characteristics suggested that of the 21 items included in the model, 5 either contributed appreciably to model fit or showed non-random patterns in their variance. Nine of the 21 items demonstrated ordered response thresholds. Results of the first pass analysis are shown in detail in Appendix V.1 (ICF Domain Construct Question List and Analyses).

Item Rescoring: The first pass analysis revealed multiple items with disordered item response thresholds, indicating a lack of uniformity in the way individuals select question response choices, such as choices "with a little trouble" and "with some trouble", or "never" and "almost never", or "almost never" and "sometimes". For items such as these with overlapping response curves, we rescored the items to combine overlapping responses into a single score. Twelve items were rescored. Following rescoring, items displayed ordered response thresholds. All items were retained in the model, resulting in a final list of 21 items representing functions related to carrying, moving and handling objects. Changes to the response scoring structure are indicated in in Appendix V.1 (ICF Domain Construct Question List and Analyses).

Second Pass Analysis

Model and Item Fit: The questions presented in the list represent a range of functions that do not directly require the ability to ambulate, and thus the analysis included responses from all participants. Available data included 2,908 scorable responses and 672 extreme scores. In the second pass analysis, the person separation index at 0.75 continued to demonstrate acceptable power of the overall model to individuate between respondents. Summary statistics showed that using the selected subset of response items to model a construct of representing manual mobility still discriminates moderately well, with a fit residual mean(SD) of 0.14(4.96), and a person fit residual mean(SD) of -0.32(1.06). Fit statistics for the final model are displayed in Table V.16. Review of individual item fit (Table V.17) suggested that of the 21 items included in the model, 3 continue to contribute somewhat to model misfit (with an item residual >|3.0|).

Table V.16. Summary Test of Fit Statistics

Item Fit	**Fit Residual Mean**	**SD**
	0.14	4.96
Person Fit	-0.32	1.06
Chi Squared Probability	1.00	
Degrees of freedom	189	
Person Separation Index (PSI)	0.75	

Table V.17. Individual Item Fit for the 21 items. Items contributing to model mis-fit are shown in BOLD.

Seq	Item	Type	Location	SE	FitResid	DF	ChiSq	DF	Prob		
1	**Q1**	**Poly**	**0.875**		**0.027**	**-7.290**		**2364.62**	**11.953**	**9**	**0.215950**
2	Q2	Poly	-0.578		0.130	0.797		86.55	0.847	9	0.999716
3	**Q3**	**Poly**	**0.717**		**0.025**	**-9.572**		**2360.54**	**15.537**	**9**	**0.077204**
4	Q4	Poly	-0.130		0.026	-0.188		2356.46	4.659	9	0.862926
5	**Q5**	**Poly**	**0.774**		**0.033**	**18.034**		**2163.76**	**47.962**	**9**	**0.000000**
6	Q6	Poly	-1.225		0.178	0.414		84.92	2.055	9	0.990567
7	Q7	Poly	-0.368		0.101	1.197		255.57	0.614	9	0.999927
8	Q8	Poly	-1.341		0.114	0.397		253.12	0.705	9	0.999868
9	Q9	Poly	-0.893		0.181	-0.244		86.55	0.894	9	0.999645
10	Q10	Poly	0.215		0.136	0.443		82.47	1.073	9	0.999250
11	Q11	Poly	0.084		0.187	1.258		68.59	1.777	9	0.994518
12	Q12	Poly	0.093		0.145	0.378		69.40	0.469	9	0.999977
13	Q13	Poly	1.975		0.220	-1.292		80.02	0.911	9	0.999617
14	Q14	Poly	-0.784		0.169	-0.211		71.04	0.822	9	0.999749
15	Q15	Poly	-1.093		0.135	2.561		86.55	1.661	9	0.995764
16	Q16	Poly	-0.231		0.185	1.798		69.40	0.668	9	0.999895
17	Q17	Poly	0.030		0.178	-0.187		82.47	0.925	9	0.999592
18	Q18	Poly	-0.887		0.035	-1.436		2298.48	10.752	9	0.293093
19	Q19	Poly	0.868		0.150	-0.974		81.65	0.573	9	0.999945
20	Q20	Poly	1.791		0.213	-1.309		80.83	1.009	9	0.999416

Individual Person Fit: Residuals values for person fit represent the difference between modelled responses and the individual's actual responses. Residual fit values < |3.0| can be considered acceptable. Residuals for individual person fit ranged from -10.6 to 2.86 (mean -0.32, SD 1.06) indicating that overall, individuals in the sample fit the model moderately well, with only 8 responses (0.27%) falling outside the acceptable range.

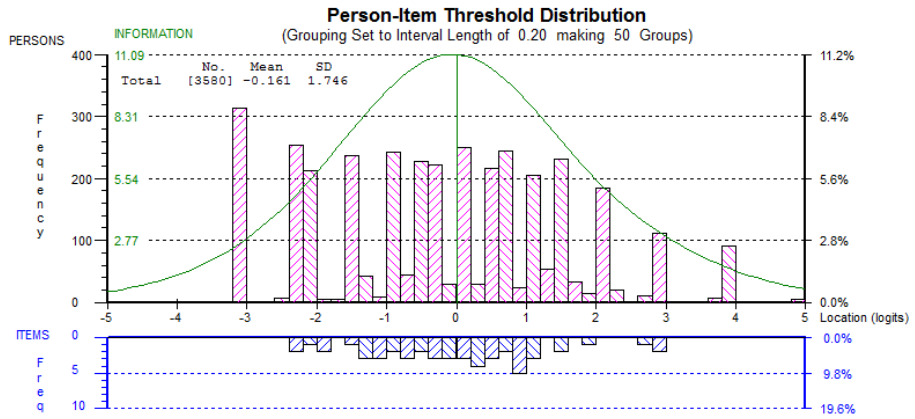
Correlation of Residuals: As noted previously, for purposes of this analysis we were willing to accept a moderate degree of correlation (ie. <0.4) between items. Items exceeding our acceptable limit of moderate residual correlation are shown in **Table V.18**. Q3 is opening a gallon of milk, which correlates with opening heavy doors. Q5 is lifting something heavy, which correlates with Q14 using scissors, Q17 opening a can of soda and Q21 opening rings on school binders. Q14 using scissors also correlates with Q16, managing footrests on a wheelchair. Taken together, the items represent different activities, although the use of scissors, opening a soda can and opening school binders are activities that require maintenance of manual dexterity but also a moderate degree of finger strength. Because the correlation between these activities is and lifting heavy objects is negative, it is likely that these items represent a continuum of strength-related activities. However, as they represent different levels of strength we have elected to include them all in the model. It may be necessary at some point to condense these items into a smaller number of questions or a single question representing strength.

Table V.18. Local Dependency for the Carrying, Moving and Handling Objects Scale Items

	Q3	Q5	Q14
Q14		-0.428	
Q16			0.406
Q17		-0.405	
Q20	0.432		
Q21		0.518	

Person-Item Threshold Location: The person-item threshold distribution shown in **Figure V.7** reflects the overall distribution of the population examined (persons in pink), in this case individuals with Duchenne muscular dystrophy, over a continuous logit scale. The distribution indictates that approximately 5% of respondents score to the right of the measurable scale (ie. ceiling effect), and slightly over 13% score to the left (ie. floor effect). This suggests that the current list does an acceptable job of assessing differences across a range of ambulatory and non-ambulatory individuals from those who are ambulatory and mildly to moderately affected to those who have lost ambulation but still retain some moderate degree of hand function to perform small manual tasks that do not require strength. When evaluated by age group, mean(SD) scores for <4, 4-6, 7-9, 10-12, 13-15, 16-18 and >18 year old participants are statistically significantly different (p=0.0000001) at 0.39(0.72), 1.03(1.46), 0.90(1.38), -0.07(1.63), -0.49(1.69), -0.94(1.66) and -1.45(1.27), respectively, in a pattern that overlaps but that is consistent with our understanding of disease progression with age in DMD. It is important to point out the slightly lower score for children under 4 years of age relative to children from 4-9 years old, and for whom it would be developmentally normal to require assistance in many of the represented tasks. When evaluated according to clinically-measured functional milestones across the entire disease severity spectrum, those differences remain pronounced between individuals who are fully functional (Group 0), those who have lost the ability to stand from supine (Group 1), those who have in addition lost the ability to climb stairs (Group 2), those who have subsequently lost the ability to rise from a chair but who remain ambulatory (Group 3), those who have lost the ability to walk but who can bring their hand to their mouth (Group 4), those who have lost the ability to bring their hand to their mouth (Group 5), and those who cannot bring their hand to their mouth and have a forced vital capacity <30% predicted (Group 6). Group mean(SD) scores for those groups are statistically significantly different (p=0.0000001) at 1.15(1.35), 0.84(1.27), 0.24(1.09), 0.02(1.20), -0.63(1.34), -1.69(1.19) and -2.10(0.76), respectively. It should be noted that while this domain does not perform well in young children whose developmental abilities are still growing, it is the only one to demonstrate an appreciable point difference between late stage individuals who are only subdivided according to respiratory function differences.

Figure V.7. Person-Item Threshold Distribution for the Carrying, Moving and Handling Objects Question Set



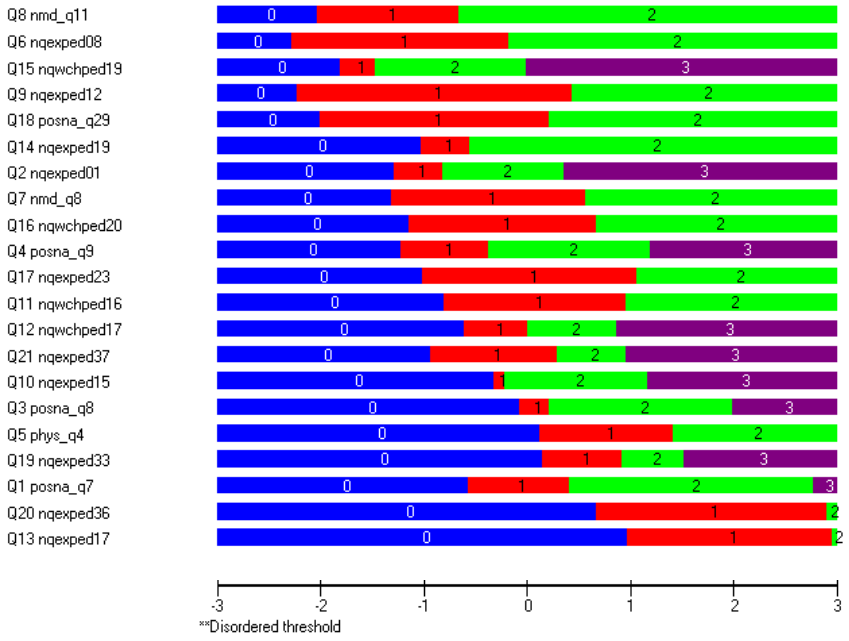
Threshold Ordering, Item Locations and Clinical "Face" Validity: Placing the questions in location order from easiest to most difficult yields the draft question set noted in **Table V.19**. The item location threshold map is presented as **Figure V.8**. Overall, these items represent a range of manual abilities that are progressively lost, starting with lifting and moving heavy objects such as heavy books, a half gallon of milk and heavy doors, followed by manual tasks such as opening school binders or soda cans or opening doors from a wheelchair, followed by opening small containers or using scissors, followed by using utencils or holding a cup. This is consistent with the clinical presentation and natural history of the disease and spans a large range of function, suggesting that our construct has face validity as a representation of manual abilities. Referring again to the apparent latent factors identified in the principle component analysis, items aligning with the first factor (tasks that require strength) predominate in the stronger end of the spectrum, while items from the second factor (tasks that require manual dexterity) predominate in the weaker end of the spectrum. Tasks associated with the third factor (tasks from a wheelchair) end up in the middle and probably represent a short period of time where individuals are wheelchair users but still have some functional degee of shoulder and elbow use. Given that the question set still demonstrates a floor effect for a portion of the population, there is a clear need for adoption of additional questions that address fine motor and hand functions such as writing ability or keyboard use.

Table V.19: Final Draft Carrying, Moving and Handling Objects Question Set

Q8 nmd_q11	It is hard to use my hands.
Q6 nquexped08	I was able to hold a full cup of water in my hand.
Q15 nqwchped19	I could manage the armrests on my wheelchair
Q9 nquexped12	I was able to use a knife to spread butter or jelly on bread
Q18 posna_q29	Turn doorknobs?
Q14 nquexped19	I was able to cut a piece of paper in half with scissors
Q2 nquexped01	I was able to open small containers like snack bags or vitamins (regular screw top)
Q7 nmd_q8	My hands are weak.

Q16 nqwchped20	I could manage the footrests on my wheelchair.
Q4 posna_q9	Open a jar that's been opened before?
Q17 nquexped23	I was able to open a can of soda
Q11 nqwchped16	I could open a door that faced away from my wheelchair
Q12 nqwchped17	I could open a door that was facing my wheelchair
Q21 nquexped37	I was able to open the rings in school binders.
Q10 nquexped15	I was able to hold a plate full of food
Q3 posna_q8	Pour a half gallon of milk?
Q5 phys_q4	Lifting something heavy
Q19 nquexped33	I was able to open a jar by myself.
Q1 posna_q7	Lift heavy books?
Q20 nquexped36	I was able to pull open heavy doors.
Q13 nquexped17	I was able to pick up a gallon of milk with one hand and set it on the table

Figure V.8: Draft Carrying, Moving and Handling Objects Question Set Item Location Threshold Map.



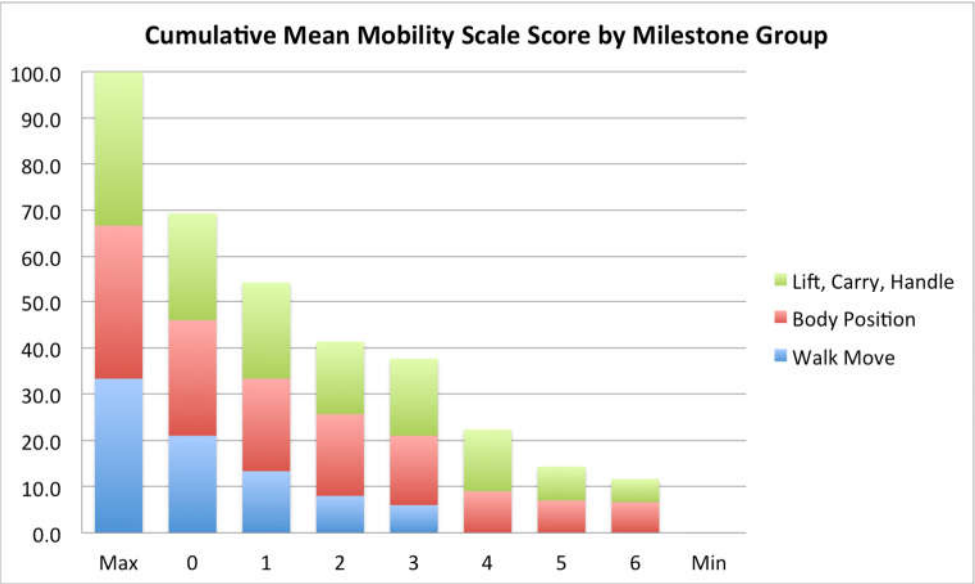
Discussion

The initial results of our evaluation of sensitivity to disease milestones and one-year change yielded a list of items that spans multiple domains within the WHO-ICF framework. Few items exist, however, that represent functions that are unrelated to neuromusculoskeletal function and movement. Certainly, the devices we selected in the Duchenne Natural History Study (DNHS) have previously demonstrated deficits among DMD patients relative to typically developing controls and other groups in non mobility-related domains such as life satisfaction, but our results suggest that, at least between contiguous milestone classification groups or over relatively short one-year periods of time, those deficits remain somewhat fixed. That those more psychosocial-oriented items failed to show differences or changes is not entirely unexpected, and there are likely to be classification schemes other than disease milestones where those items might demonstrate change over time.

Subsequently, we focus on a set of items that have demonstrated sensitivity to disease and one-year change which correspond to the mobility subdomain domain of the WHO-ICH Activities and Participation domain and describe arm, leg and trunk functions that are progressively lost during the course of Duchenne muscular dystrophy. We have demonstrated that despite the continuing existence of ceiling and floor effects in each of the three person-reported mobility-oriented domain scores discussed above, they describe a continuum of individuals with Duchenne muscular dystrophy across most of the currently observed range of ages and stages of disease who we have profiled in the DNHS (19, 21). Furthermore, taken together, the scales provide a patient (or patient proxy)-assessed range of functional ability of the arms, legs and trunk that ranges from newly diagnosed and nearly typical-appearing young children to severely impaired young adults at the end of their expected life span. Through the Rasch analysis approach and comparison with previously described functional milestones that are progressively and predictably lost as the disease progresses, we have demonstrated the initial psychometric characteristics and clinical validity of each scale, and provided initial estimates of mean linearized mobility domain scores for each functional milestone group.

While each of the mobility domain scores may be useful in its own right, the power of this approach is in the development of a combined and linear mobility score that can be used across the entire range of functional abilities associated with the disease. Figure V.9 below provides a look at one potential method of achieving this such a combined score. By converting each of the three mobility domain logit location ranges to a simple 0-100 point scale (with 100 representing best function and 0 representing worst), we are able to then combine all three scores to create an average mobility score for each milestone group. As depicted below then, individuals at near full function in Milestone Group 0 have average score of 70 points, with each mobility domain contributing approximately 1/3 of the total score. As milestones are progressively lost, we see that on average the functions described in the Walking and Moving domain are lost first, followed by a gradual and somewhat proportional loss of the Maintaining Body Position and Carrying, Moving and Handling Objects domain functions.

Figure V.9M



Revisions to Question Syntax and the Response Structure

While this combined scale initially appears to possess the desirable qualities of being a continuous assessment scale that can be used across the entire span of ages and stages of the disease, the three domains still have mis-fitting items and ceiling and floor effects that could be optimized through revisions to the question set, but with respect to item content and presentation. First, it appears that overall, the items derived from the PODCI device continue to yield high fit residuals, suggesting that there may be a moderate degree of subjectivity in the way that patients select their responses. In comparison, items from the NeuroQOL devices more frequently demonstrate acceptable fit residuals, suggesting that they are answered in a much more predictable pattern as the disease progresses. We have previously noted that the lack of responsiveness of the PedsQL relative to 6-minute walk velocity may be due in part to the wording of the questions such that they ask "In the past 7 days, *how much of a problem* has it been for you to..." (responses Never, Almost Never, Sometimes, Often, Almost Always), while the more responsive PODCI instrument asks questions in the manner of "During the last week, has it been easy or hard for you to…" (responses Easy, A Little Hard, Very Hard, Can't Do) (24). While this is a subtle difference, the former adds a subjective aspect of whether an activity is desirable in addition to it's level of difficulty, while the PODCI items simply ask about overall difficulty. Here with respect to the PODCI versus the NeuroQOL, we may be seeing a similar effect. Items from the NeuroQOL scales underwent extensive testing, response revision and cognitive debriefing prior to publication using the syntax "In the past 7 days, I could _____ (responses With no trouble, With a little trouble, With some trouble, With a lot of trouble". It is apparent from our rescoring efforts to correct disordered response thresholds on many of our items that there is still some inconsistency in differentiating between "With a little trouble" and "With some trouble", and this question style lacks a "can't do at all" response, but it may be appropriate to revise the questions to reflect a combination of PODCI and NeuroQOL styles, with a syntax that reads: In the past 7 days, I could _____ (responses With no trouble, With some trouble, With a lot of trouble, Can't do).

In addition to revision of individual question presentation, our mixed use of instruments across different ages has resulted in the retention of multiple items that are from different instruments but that relate to the same overall concept. For instance, use of the PODCI and NeuroQOL in different groups has given us one question about getting in and out of bed, one question about getting into bed, and one question about getting out of bed. These items, naturally, are highly co-dependent, and ideally only one would be left in the final model. Further Rasch analysis following a uniform application of these questions to an entire (planned) future cohort will allow us to simplify the model even more.

A third type of question adjustment that we can approach will be consolidation of questions regarding similar tasks at different levels of difficulty. For instance, the NeuroQOL question "I was able to open a jar by myself" and the PODCI item "Open a jar that's been opened before" represent similar functions and load on the same factor according to principle component analysis, but the latter aligns further down the scale with easier items relative to the former. We may be able to use the factor loadings and question content as a guide to combine questions with a syntax similar to:

In the past 7 days, I could open a jar if:

1) Easily, even if it had never been opened
2) Easily, if it had been opened before
3) With some difficulty, if it had been opened before
4) With a lot of difficulty, if it had been opened before
5) Can't do

Comparable instruments from clinical practice: The North Star Ambulatory Assessment, Egen Klassifikation Scale, and Performance of the Upper Limb (PUL) Assessment.

Another issue with the domain item lists as presented at this point is the continued existence of ceiling and floor effects in all three mobility domains. In the Walking and Moving item list, questions represent a wide range from difficult (walking more than a mile) to easy (walking between rooms). In the Changing and Maintaining Body Position list, tasks range from difficult (getting out of a chair without using one's arms) to easy (moving one's head to look to the side). In the Carrying, Moving and Handling Objects list, tasks range from difficult (picking up a gallon of milk) to easy (holding a cup of water). However, we can readily develop candidate items on the more difficult and easier ends of these scales by referring to some of the analogous validated functional clinical examinations that are currently in use. The North Star Ambulatory Assessment (NSAA) contents are similar to those from the Walking and Moving item list; the Egen Klassifikation (EK) Scale is similar in content to the Changing and Maintaining Body Position list; and the Performance of the Upper Limb (PUL) Assessment is similar to the Carrying, Moving and Handling Objects list.

Both the NSAA and the PUL were developed using Rasch techniques for construction and validation tools (22, 23). Mayhew and colleagues collected cross-sectional NSAA assessment data from the North Star database for 191 ambulatory boys with DMD between 3-15 years of age and examined properties of the instrument that included clinical meaningfulness, appropriateness of item targeting, order of item response categories, Rasch model fit, and instrument reliability and stability. A copy of the NSAA device is attached for reference as Appendix V.2. They determined that Rasch analysis upheld reliability and validity of the instrument as a measure of mobility and ambulatory function in DMD that logically follows functional loss resulting from disease progression. Furthermore, they described an s-shaped logistic curve relationship for a transformation scale between raw scores and logit-based location on the continuous Rasch-based scale. That function illustrated that raw scale scores yield different continuous interval score changes over the possible range of instrument, with continuous score changes that are magnified at both tails of the distribution relative to the middle. In a longitudinal follow up paper, Mayhew used a similar cohort of 198 DMD patients between 4 and 18 years of age from the North Star database to examine NSAA responsiveness to disease progression over time and minimal clinically-important difference (MCID) of mean scores for GC-treated and GC-naïve patients (25). They also reported a 0-100 point logit transformed scale relative to the 0-32-point NSAA raw score scale. In both GC-treated and GC-naïve patients, they showed the instrument is responsive to previously described improvements in ambulatory ability scores for children under 7 due to milestone attainment during the early childhood growth spurt (26, 27), as well as functional loss due to disease progression over the range of individuals in the sample. Importantly, they also demonstrated that by linearizing items on the Rasch model scale, distribution-based minimal clinically important differences in score across the range of function can be directly linked to loss of specific functional abilities. The authors illustrated this by demonstrating that a change from a score of 50 to 40 on the transformed scale directly corresponds to loss of ability to rise from the floor without assistance.

The EK scale was developed by the Danish muscular dystrophy association as a clinical tool to assess overall functional ability in the non-ambulatory DMD population(28, 29). This tool includes assessments comprised of functional assessments measuring interaction of physical components such as muscle strength, range of motion, respiratory status, wheelchair dependence and age. The Scale assesses ten functional categories (EK 1-10), each contributing to an overall picture of function. A copy of the EK Scale device is attached for reference as Appendix V.3

Mayhew et al also developed the upper limb assessment tool called the Performance of the Upper Limb module for Duchenne muscular dystrophy (22). A copy of the PUL device is attached for reference as Appendix V.4. The device was developed using upper limb functional performance items from the Brooke upper extremity functional scale (5), the Jebsen-Taylor Hand Function Test (JTHFT) (30) and the Motor Function Measure (MFM)(31) selected on the basis of a conceptual framework that items should provide assessment of upper limb and hand mobility including impact of weakness, growth and development of joint contractures across both ambulatory and non-ambulatory phases of disease. Item selection by a key informant workgroup of clinicians occurred following assessment using the full instrument measures performed on 61 volunteers with DMD 11-30 years of age. The resulting item list was then assessed in 86 volunteers with DMD between 5-27 years of age. Rasch analysis of the pilot instrument data demonstrated excellent item fit and good reliability, with some collapsing of disordered item responses into broader but clinically appropriate categories. Development of the PUL instrument is ongoing. Application of Rasch analysis using the two clinician-

reported outcome scales, both of which represent different aspects of mobility, strongly suggests the utility of evaluating similarly constructed items from commonly used patient-reported instruments alone or in combination with clinically-obtained assessments.

Item list-specific recommendations for instrument development.

Using the Rasch analysis-derived feedback on item syntax and response category characteristics, and using the three clinical measurement instruments as guides to examine other possible elements of mobility function specific to DMD, as well as possible mobility functions that may exist outside of our currently appreciated ceiling and floor effects, we can make specific recommendations regarding future modifications of each mobility domain item list.

Walking and Moving: In the walking and moving list, we see that there are several high-residual items from the PODCI instrument. In addition, we have multiple items from the NeuroQoL that are missing a "Can't Do" response category. As discussed above, we should consider revising the question set so that items follow a format so that items are phrased as "In the past 7 days, I could _____" (responses With no trouble, With some trouble, With a lot of trouble, Can't do). This rephrasing should help to improve disordered responses by reducing ambiguity in the light to moderate difficulty responses, and may also help somewhat in extending the "floor" of the scale by accounting for individuals who cannot do the tasks. The title of the scale itself dictates the items that it addresses, and "Walking and moving" as a construct related to strength really only applies to those who are ambulatory to some degree. Wheelchair mobility items, on the whole, are not sensitive to changes in disease status / milestone, at least as defined here. Some of the questions we evaluated are aimed at manual wheelchair use, and some at power wheelchair use, and it's likely that there's a differential response between users of one technology vs. another, though we don't have the data to examine this here. There is likely a relationship with distal/hand ability and wheelchair driving, but technologies related to power wheelchair mobility are continuously evolving, and even individuals with very severe strength limitation are generally able to move about in their power chairs fairly easily. Wheelchair mobility should be a topic of discussion in future instrument development, to see whether any important topic areas emerge, and to develop some pilot questions. It also remains unclear whether wheelchair mobility, as an activity that is dictated by access to technology rather than disease progression specifically, represents a true physical mobility domain or more accurately reflects activity and participation – for example, it is hard to imagine that wheelchair mobility would be tested as an endpoint in a clinical trial of a drug to improve overall function. However, within the ambulatory group of patients, we can look to the North Star Ambulatory Assessment tool for suggestions on items that are easier (ie. to the left of the item thresholds) to address floor effects, and more difficult items (ie. to the right of the item thresholds) to address ceiling effects. When compared to the NSAA (Table V.20), our questions address NSAA functions of running, walking, climbing a box step, and descending a box step. On the easier end of the spectrum, the NSAA grades the lowest level of walking function as Walking Grade 0: "Loss of independent ambulation – may use KAFOs or walk short distances with assistance." Our most difficult question "I could walk between rooms" is from the NeuroQOL and thus the most difficult response was "With a lot of trouble". As suggested by the NSAA scoring paradigm, addition of a "Can't do" response as noted above may then be expected to lower the "floor" of the instrument somewhat. On the most difficult end of the spectrum, our hardest question is "Walk more than a mile". Here it is instructive to look at the NSAA items (Table V.21) that are not represented in our current list, including jumping, hopping, standing on the heels, standing on one leg, and lifting the head while supine – all functions that have been noted as early deficits in children with DMD, and which may show to be more difficult than a one-mile walk. With the exception of the last item (lifting the head), all of these functions appear at face value to relate directly in some way to ambulatory ability – a model that has been validated by Mayhew and colleages through their Rasch analysis of the NSAA instrument. Some children with DMD never attain the ability to hop on one foot, and thus addition of questions targeted to these four functions thus may extend the range of the question set to cover the entire young and more functional end of the DMD spectrum. From a standpoint of simplification and consolidation of multiple questions into a single item with responses directed at multiple levels of ability, it may be helpful for us to look at how the questions in our subscale are related to the items in the clinical scale (Table V.20). For instance, our question items that fall under the NSAA Item 6 and 7: Climbing and Descending steps domain may be appropriate to consolidate into a single item that reflects to perform climbs of increasing height and/or duration.

Table V.20. Items linking the North Star Ambulatory Assessment and the Walking and Moving Scale.

NSAA Item 2: Walking.
2 - Walks with heel-toe or flat-footed gait pattern
1 - Persistent or habitual toe walker, unable to heel-toe consistently
0 - Loss of independent ambulation – may use KAFOs or walk short distances with assistance

Linking Items (In order of difficulty)

Q5	nqmobped05	I could walk between rooms
Q13	nqmobped21	I could walk on slightly uneven surfaces (such as cracked pavement)
Q18	nqmobped24	I could walk on rough, uneven surfaces (such as lawns, gravel driveway)
Q17	posna_q44	Walk one block?
Q1	nqmobped01	I could keep my balance while walking for 30 minutes
Q4	nqmobped04	I could walk for 15 minutes

Q19 nqmobped25 I could walk up and down ramps or hills
Q16 posna_q43 Walk three blocks?
Q6 nqmobped12 I could walk for 30 minutes
Q14 posna_q42 Walk more than a mile?

NSAA Item 6, 7: Climb Box Step
2 - Faces step – no support needed
1 - Goes up sideways or needs support
0 - Unable

NSAA Items 8, 9: Descend Box Step
2 - Faces forward, climbs down controlling weight bearing leg. No support needed
1 - Sideways, skips down or needs support
0 - Unable

Linking Items
Q20 nqmobped26 I could walk up and down curbs
Q12 posna_q41 Climb one flight of stairs?
Q23 nqmobped39 I could walk up 2-3 stairs
Q9 posna_q40 Climb three flights of stairs?

NSAA Item 17: Run (10m)
2 - Both feet off the ground (no double stance phase during running)
1 - 'Duchenne jog'
0 – Walk

Linking Item
Q7 posna_q38 Run short distances?

Table V.21. Functions from NSAA that are missing in the Walking and Moving item list.

NSAA Item 5: Stand on one leg.
2 - Able to stand in a relaxed manner (no fixation) for count of 3 seconds
1 - Stands but either momentarily or needs a lot of fixation e.g. by knees tightly adducted or other trick
0 – Unable

NSAA Item 12: Lifts head
2 – In supine, head must be lifted in mid-line. Chin moves toward chest
1 – Head is lifted but through side flexion or with no neck flexion
0 – Unable

NSAA Item 13: Stands on heels
2 – Both feet at the same time, clearly standing on heels only (acceptable to move a few steps to keep balance) for count of 3
1 – Flexes hip and only raises forefoot
0 – Unable

NSAA Item 14: Jump
2 – Both feet at the same time, clear of the ground simultaneously
1 – One foot after the other (skip)
0 – Unable

NSAA Item 15, 16: Hop
2 – Clears forefoot and heel off floor
1 - Able to bend knee and raise heel, no floor clearance
0 - Unable

Changing and Maintaining Body Position: In the changing and maintaining body position list, we see that there are several high-residual instruments from the PODCI instrument. In addition, we have multiple items from the NeuroQoL that are missing a "Can't Do" response category. As discussed above, we should consider revising the question set so that items follow a format so that items are phrased as "In the past 7 days, I could _____" (responses With no trouble, With some trouble, With a lot of trouble, Can't do). This rephrasing should help to improve disordered responses by reducing ambiguity in the light to moderate difficulty responses, and may also help somewhat in extending the "floor" of the scale by accounting for individuals who cannot do the tasks. Extension of the "floor" of the scale may also be informed through comparison of the current question items to items contained in the EK scale (Table V.22). When compared to the EK scale, our questions address functions of standing, transferring to and from a wheelchair, balancing in a wheelchair (or chair), moving the arms, turning in bed, and head control. On the easier end of the spectrum, the EK scale grades the lowest level of head control as Head Control Grade 3 – "When sitting still in a wheelchair needs head support". Our most difficult question "I could turn my head all the way to the side to look at someone or something" is from the NeuroQOL and thus the most difficult response was "With a lot of trouble". As we have previously noted, addition of a "Can't do" response may then be expected to lower the "floor" of the instrument somewhat. In addition, it is instructive to look at the other high-difficulty responses from the EK scale questions that are represented here. Other difficult items that might lower the instrument floor might include items from the

wheelchair transfer question (Grade 2 - Needs assistance to transfer with or without additional aids; Grade 3 - Needs to be lifted with support of the head when transferring from wheelchair), Ability to balance in the wheelchair (Grade 3 – Unable to change position of the upper part of the body, cannot sit without total support of the trunk or head), Ability to turn in bed (Grade 2 – Unable to turn himself in bed. Has to be turned 0-3 times per night; Grade 3 – Unable to turn himself in bed, Has to be turned >4 times per night), and head control (Grade 3 – When sitting still in a wheelchair needs head support). Other items in the EK scale that are not represented in this question set (Table V.23) are primarily concerned with other functions not directly related to body position control but that may be instructive when considering hand and arm function (refer to the next section). On the most difficult end of the spectrum, our hardest question is "I could get on and off a chair without using my arms". The EK scale was developed as a tool for non-ambulatory individuals, and thus in this instance is not very informative. However when we examine disease-related milestones we can see that loss of the ability to stand from supine precedes loss of ability to rise from a chair, and thus the NSAA item 11: Rise from floor becomes relevant, as rising from supine can be considered a positional transfer. Addition of an item on the "difficult" end of the scale that addresses not only overall ability to rise from the floor, but the quality of such a motion may extend the "ceiling" of the instrument in the direction of more functional individuals. A question such as "In the past 7 days, I could stand from the floor without putting my hands on my knees" (responses With no trouble, With some trouble, With a lot of trouble, Can't do) might be effective at identifying children who can still stand without evidence of the classic "Gower's manoeuvre" that is an early tell tale sign of early disease progress. From a standpoint of simplification and consolidation of multiple questions into a single item with responses directed at multiple levels of ability, it may be helpful for us to look at how the questions in our subscale are related to the items in the clinical scale (Table V.22). For instance, our bed, chair or toilet question items that fall under the EK Item 2: Ability to transfer from wheelchair domain may be appropriate to consolidate into a single item that reflect similar transfers of varying degrees of difficulty.

TABLE V.22. Items linking the NSAA and EK Scale and the Changing and Maintaining Body Position item list.

NSAA Item 11: Rise from floor
- 2 – From supine, no evidence of Gower's manoeuvre
- 1 – Gower's evident
- 0 – Needs external support object (eg. Chair) or unable

Linking Items

Q9	nqmobped13	I could get up from the floor by myself

EK Item 2: Ability to transfer from wheelchair
- 0 – Able to transfer from wheelchair without help
- 1 – Able to transfer independently from wheelchair, with use of aid
- 2 – Needs assistance to transfer with or without additional aids (hoist, easy-glide)
- 3 – Needs to be lifted with support of the head when transferring from wheelchair

Linking Items

Q24	nqexped31	I was able to get into bed by myself.
Q23	posna_q28	Get in and out of bed?
Q22	nqexped30	I was able to get out of bed by myself.
Q2	nqwchped04	I could move between my wheelchair and another seat such as a chair or bed
Q3	nqwchped06	I could manage getting on and off the tub bench from a wheelchair
Q4	nqwchped07	I could manage getting on and off the toilet from a wheelchair
Q5	nqwchped08	I could stand up from an armless straight chair using my wheelchair
Q7	nqmobped10	I could get in and out of an adultsized chair
Q21	posna_q27	Get on and off a toilet or chair?
Q6	nqmobped09	I could get on and off a low chair
Q8	nqmobped11	I could get on and off a chair without using my arms.

EK Item 3: Ability to Stand
- 0 – Able to stand with knees supported, as when using braces
- 1 – Able to stand with knees and hips supported, as when using standing aids
- 2 – Able to stand with full body support
- 3 – Unable to stand or be stood

Linking Items

Q19	posna_q25	Stand while washing his hands and face at a sink?
Q27	posna_q31	How often did your child need help from another person for sitting and standing?

EK Item 4: Ability to balance in the wheelchair
- 0 – Able to push himself upright from complete forward flexion by pushing up with hands
- 1 – Able to move the upper part of the body >30 degrees in all directions from the upright position, but cannot push himself upright as above
- 2 – Able to move the upper part of the body <30 degrees from one side to the other
- 3 – Unable to change position of the upper part of the body, cannot sit without total support of the trunk or head.

Linking Items

Q11	nqmobped15	I could sit on a bench without back support for 30 minutes

EK Item 5: Ability to move the arms
- 0 – Able to raise the arms above the head with or without compensatory movements
- 1 – Unable to lift the arms above the head, but able to raise the forearms against gravity (ie. hand to mouth with/without elbow support)
- 2 – Unable to lift the forearms against gravity, but able to use the hands against gravity when the forearm is supported
- 3 – Unable to use the hands against gravity, but able to use the fingers

Linking Items
Q16 nqexped21I was able to cover my nose when sneezing

EK Item 7: Ability to turn in bed
0 – Able to turn himself in bed when under bed sheets or cover
1 – Needs some help to turn in bed or can turn in some directions
2 – Unable to turn himself in bed. Has to be turned 0-3 times per night.
3 – Unable to turn himself in bed. Has to be turned >4 times per night.
Linking Items
Q12 nmd_q16 It is hard to turn myself during the night.
Q17 nqexped26I was able to change positions in my bed

EK Item 12: Head control
0 – Does not need head support
1 – Needs head support when going up and down slope (15 degree standard ramp)
2 – Needs head support when driving wheelchair
3 – When sitting still in a wheelchair needs head support
Linking Items
Q15 nqmobped19 I could turn my head all the way to the side to look at someone or something

Table V.23. Functions from the EK Scale that are missing in the Changing and Maintaining Body Position item list.
EK Item 1: Ability to Use a Wheelchair
0 – Able to use a manual wheelchair on flat ground (10m < 1 minute)
1 - Able to use a manual wheelchair on flat ground (10m > 1 minute)
2 – Unable to use manual wheelchair, requires power wheelchair
3 – Uses power wheelchair, but occasionally has difficulty steering
EK Item 6: Ability to use hands and arms for eating
0 – Able to eat and drink without elbow support
1 – Eats or drinks with support at elbow
2 – Eats and drinks with elbow support; with reinforcement of the opposite hand + or – aides
3 – Has to be fed
EK Item 8: Ability to cough
0 – Able to cough effectively
1 – Has difficulty to cough and sometimes needs manual reinforcement. Able to clear throat.
2 – Always needs help in coughing. Only possible to cough in certain positions.
3 – Impossible to cough, needs suction and/or hyperventilation techniques or IPPB in order to keep airways clear
EK Item 9: Ability to speak
0 – Powerful speech, able to sing and speak loudly
1 – Speaks normally, but cannot raise his voice
2 – Speaks with a quiet voice, and needs a breath after 3-5 words
3 – Speech is difficult to understand, except to close relatives
EK Item 10: Physical well-being
0 – No complaints, feels good
1 – Easily tires, has difficulty resting in a chair or bed
2 – Has loss of weight, loss of appetite, scared of falling asleep at night, sleeps badly
3 – Experiences additional symptoms: change of mood, stomach ache, palpitations, perspiring
EK Item 11: Daytime fatigue
0 – Doesn't get tired during the day
1 – Need to limit activity to avoid getting too tired
2 – Need to limit activity *and* have a rest period to avoid getting too tired
3 – Get tired during the day even if I rest and limit activity
EK Item 13: Ability to control joystick
0 – Uses a standard joystick without adaptation
1 – Uses an adapted joystick or has adjusted wheelchair in order to use joystick
2 – Uses other techniques for steering than joystick such as blowing sucking systems or scanned driving
3 – Unable to operate wheelchair, needs another person to operate it
EK Item 14: Food Textures
0 – Eats all textures of food
1 – Eats cut up/chunky food or avoids hard/chewy foods
2 – Eats minced/pureed food with supplementation as required
3 – Main intake consists of being tube fed
EK Item 15: Eating a meal
0 – Able to consume a whole meal in the same time as others sharing the meal
1 – Able to consume a whole meal in the same time as others only with encouragement or needs some additional time (approximately 10 minutes)
2 – Able to consume a whole meal but requires substantially more time compared to others eating the same meal (15 minutes or more extra)
3 – Unable to consume a whole meal
EK Item 16: Swallowing
0 – Never has problems when swallowing, and never chokes on food/drink
1 – May experience occasional (less than once a month) problems swallowing certain types of food or occasionally chokes
2 – Has regular trouble swallowing food/drink or chokes on food/drink (more than once a month)
3 – Has trouble swallowing saliva or secretions
EK Item 17: Hand function
0 – Can unscrew the lid of a water or fizzy drink bottle and can break the seal
1 – Can write two lines *or* use the computer keyboard
2 – Can write signature *or* send text *or* use remote control

3 – Cannot use hands

Carrying, Moving and Handling Objects: In the carrying, moving and handling objects list, we once again see that there are high-residual instruments from the PODCI instrument. In addition, we have multiple items from the NeuroQoL that are missing a "Can't Do" response category. As discussed above, we should consider revising the question set so that items follow a format so that items are phrased as "In the past 7 days, I could _____" (responses With no trouble, With some trouble, With a lot of trouble, Can't do). This rephrasing should help to improve disordered responses by reducing ambiguity in the light to moderate difficulty responses, and may also help somewhat in extending the "floor" of the scale by accounting for individuals who cannot do the tasks. Extension of the "floor" of the scale may also be informed through comparison of the current question items to items contained in the PUL Assessment (Table V.24). When compared to the PUL Assessment, our questions address functions of lifting heavy weights, opening containers, holding items while supinating the hand, and fine motor ability. On the more difficult end of the spectrum, the PUL assessment contains multiple hand functions relating to fine motor control that may fall below our weakest items of "It's hard to use my hands" (Table V.25). These items include tearing paper, tracing a path with a pencil, pushing on a light switch, placing a finger on a number diagram, and pinch, 3-point and thumb grips. All of these functions are maintained until very late in disease progression, and developing questions to address similar daily tasks would be expected to extend the "floor" of our instrument to a much larger number of very weak individuals. In fact, recent Rasch analysis results of the development of the Person Reported Measure Upper Limb (PROM UL) by Katrijn Klingel (PROM-UL development group meeting, June 10 2015) reveal a list of upper extremity functional tasks that extend far past our current set of items on the weak end of the spectrum. Question items, which range from "Screw the cap off a bottle that has not been opened before" (strong end) to "Use a TV remote control" are presented in Table V.26. In her presentation, Dr. Klingel noted an outlier group on the stronger end of the scale. This makes sense when we combine our list and the PROM-UL items in order from easiest to most difficult (Table V.27). We see that the order of tasks is somewhat in agreement, with considerable overlap in the middle of the spectrum. As noted, PROM-UL items cover the weaker end of the spectrum, and our items cover the stronger end. We still observe a ceiling effect that produces outlier individuals on the stronger end of the spectrum. However, in considering additional questions on the stronger end, we may be able to look to the PUL Assessment items that evaluate shoulder function, namely shoulder abduction and flexion to at or above shoulder height, and identify daily activities that might require that type of motion. These may involve high level tasks such as brushing hair, scratching the top of the head, or reaching for highly placed objects. Some of the shoulder-height tasks may already be represented by our questions regarding ability to open doors (doorknobs are often at shoulder height for children and individuals in wheelchairs), but that will require further evaluation. From a standpoint of simplification and consolidation of multiple questions into a single item with responses directed at multiple levels of ability, it may again be helpful for us to look at how the questions in our subscale are related to the items in the clinical scale (Table V.25). For instance, our container opening question items that fall under the PUL Item M: Remove lid from container heading may be appropriate to consolidate into a single item that reflect similar tasks of varying degrees of difficulty.

Table V.24. Items linking the PUL and the Changing and Carrying, Moving and Handling Objects item list.

PUL Item H: Move weight on table
- 5 – Can lift 1kg weight from outer to centre circle without compensation
- 4 - Can lift 500g weight from outer to centre circle without compensation
- 3 - Can lift 200g weight from outer to centre circle without compensation
- 2 - Can lift 100g weight from outer to centre circle without compensation
- 1 - Can slide 100g weight from outer to centre circle without compensation
- 0 - Unable

Linking Items

Q5 phys_q4	Lifting something heavy
Q1 posna_q7	Lift heavy books?

PUL Item J: Lifting Heavy Cans
- 5 – Lift 5 (furthest away from preferred) [Note this is across body midline]
- 4 – Lift 4
- 3 – Lift 3 (Centre)
- 2 – Lift 2
- 1 – Lift 1 (Outer)
- 0 - Unable

Linking Items

Q6 nquexped08	I was able to hold a full cup of water in my hand.
Q3 posna_q8	Pour a half gallon of milk?
Q13 nquexped17	I was able to pick up a gallon of milk with one hand and set it on the table

PUL M: Remove Lid from Container
- 1 – Opens completely
- 0 – Unable to open

Linking Items

Q2 nquexped01	I was able to open small containers like snack bags or vitamins (regular screw top)

Q17 nquexped23 I was able to open a can of soda
Q4 posna_q9 Open a jar that's been opened before?
Q19 nquexped33 I was able to open a jar by myself.

PUL Item Q: Supination
4 – Picks up the light, and turns the hand over completely without any compensatory movements
3 – Picks up the light and turns it over completely with compensatory movements
2 – Picks up the light and turns the hand over incompletely
1 – Picks up the light but cannot turn the hand over
0 – Cannot pick up the light

Linking Items
Q10 nquexped15 I was able to hold a plate full of food

PUL Item R: Picking up coins
3 – Can pick up and hold six coins in one hand
2 – Can pick up and hold three coins in one hand
1 – Can pick up one coin
0 – Cannot pick up one coin

Linking Items
Q8 nmd_q11 It is hard to use my hands.
Q7 nmd_q8 My hands are weak.

Table V.25. Functions from the PUL Assessment that are missing in the Carrying, Moving and Handling Objects item list.

PUL Item B: Shoulder abduction to shoulder height
4 – 1000g
3 – 500g
2 – 200g
1 – Able, no weights
0 – Unable

PUL Item C: Shoulder abduction above shoulder height
4 – 1000g
3 – 500g
2 – 200g
1 – Able, no weights
0 – Unable

PUL Item D: Shoulder flexion to shoulder height
4 – 1000g
3 – 500g
2 – 200g
1 – Able, no weights
0 – Unable

PUL Item D: Shoulder flexion above shoulder height
4 – 1000g
3 – 500g
2 – 200g
1 – Able, no weights
0 – Unable

PUL Item F: Hand to mouth
3 – Able to bring 200g in cup to mouth with one hand and no elbow support
2 – Able to bring 200g in cup to mouth either with 2 hands or one hand with elbow support
1 – Able to bring 50g in cup to mouth using 2 hands
0 – Unable

PUL Item G: Hand(s) to table from lap
3 – Two hands completely and simultaneously to table
2 – Two hands completely on table but not at same time
1 – Gets both hands on table but incompletely
0 – Unable

PUL Item I: Lifting light cans
5 – Lift 5 (furthest away from preferred) [Note this is across body midline]
4 – Lift 4
3 – Lift 3 (Centre)
2 – Lift 2
1 – Lift 1 (Outer)
0 – Unable

PUL Item K: Stacking Light Cans

5 – Stack 5th can
4 – Stack 4th can
3 – Stack 3rd can
2 – Stack 2nd can
1 – Unable to stack 2nd can

PUL Item L: Stacking Heavy Cans
5 – Stack 5th can
4 – Stack 4th can
3 – Stack 3rd can
2 – Stack 2nd can
1 – Unable to stack 2nd can

PUL Item N: Tearing paper
4 – Tears the sheet of paper folded in 4, beginning from the fold edge
3 - Tears the sheet of paper folded in 2, beginning from the fold edge
2 – Tears the unfolded sheet of paper
1 – Can hold unfolded sheet of paper but cannot tear it
0 – Cannot hold paper or tear it

PUL Item O: Tracing path
4 – Able to pick up pencil and able to complete the path without stops or raising hand from paper
3 – Able to complete the path but needs to stop or raises hand from paper
2 – Able to follow the path for at least 5cm but unable to complete the path
1 – Able to hold pencil and can make a mark on the paper
0 – With pencil in hand unable to hold it or to make a mark

PUL Item P: Push on the light
3 – Able to turn the light on permanently with one hand
2 – Able to turn the light on momentarily with one hand
1 – Able to turn the light on momentarily with two hands
0 – Unable to turn the light on momentarily with two hands

PUL Item S: Place finger on number diagram
3 – Raises finger and places it successively on the numbers of the diagram without touching the lines
2 – Raises finger and places it imprecisely on the numbers
1 – Cannot raise finger to place it on a drawing but can slide it between at least two squares
0 – Cannot raise finger or slide it on the diagram

PUL Item T: Finger pinch grip
2 – Able to finger pinch and lift weight
1 – Able to achieve finger pinch grip but can't move weight
0 – Unable to achieve finger pinch grip

PUL Item U: 3 point grip
2 – Able to 3 point grip and lift weight
1 – Able to achieve 3 point grip but can't move weight
0 – Unable to achieve 3 point grip

PUL Item V: Thumb (key) grip
3 – Able to grip and lift weight
2 – Able to achieve thumb grip but can't lift weight
1 – Unable to achieve thumb grip but can move end of thumb
0 – Unable to achieve thumb grip or bend end of thumb

Table V.26: PROM Items by Order of Difficulty, easiest to hardest (Katrijn Klingels' slide presentation, Rome UL meeting, June 10, 2015)

Use a TV remote control
Use a mouse
Type on a computer with a keyboard
Sign name
Turn the pages of a book
Pick up small objects from the table
Dial/Text on a cell phone (this may be adapted to "use a touchscreen")
Eat a meal
Press buttons on an elevator
Open a drawer
Turn a light switch on/off on the wall at a standard height
Drink from a half-full glass without a straw
Reach out to shake hands
Bring a phone to your ear
Wash hands
Write several lines
Wipe nose
Brush teeth

Take money from a wallet from your pocket to pay for something
Scratch head
Take a book out of a bag on your lap
Open a fridge door
Open a pack of crisps (chips)
Pour a drink from a half-liter bottle
Fasten a zipper
Cut up different textures of food
Pick up a pen from the floor
Put a jacket on
Button up (a shirt for example)
Pull up trousers after using the toilet
Open a can of soft drink
Screw the cap off a bottle that has not been opened before

Table V.27: Combined items from the Carrying, Moving and Handling Objects scale and the experimental PROM-UL device (bold), in apparent order from easiest to most difficult

Use a TV remote control
Use a mouse
Type on a computer with a keyboard
Sign name
Turn the pages of a book
Pick up small objects from the table
Dial/Text on a cell phone (this may be adapted to "use a touchscreen")
Q8 nmd_q11 It is hard to use my hands.
Q6 nquexped08 I was able to hold a full cup of water in my hand.
Q15 nqwchped19 I could manage the armrests on my wheelchair
Q9 nquexped12 I was able to use a knife to spread butter or jelly on bread
Eat a meal
Q18 posna_q29 Turn doorknobs?
Q14 nquexped19 I was able to cut a piece of paper in half with scissors
Press buttons on an elevator
Open a drawer
Turn a light switch on/off on the wall at a standard height
Drink from a half-full glass without a straw
Reach out to shake hands
Bring a phone to your ear
Wash hands
Write several lines
Wipe nose
Brush teeth
Take money from a wallet from your pocket to pay for something
Scratch head
Take a book out of a bag on your lap
Open a fridge door
Q2 nquexped01 I was able to open small containers like snack bags or vitamins (regular screw top)
Open a pack of crisps (chips)
Pour a drink from a half-liter bottle
Fasten a zipper
Cut up different textures of food
Pick up a pen from the floor
Put a jacket on
Button up (a shirt for example)
Pull up trousers after using the toilet
Q7 nmd_q8 My hands are weak.
Q16 nqwchped20 I could manage the footrests on my wheelchair.
Q4 posna_q9 Open a jar that's been opened before?
Open a can of soft drink
Q17 nquexped23 I was able to open a can of soda
Q11 nqwchped16 I could open a door that faced away from my wheelchair
Q12 nqwchped17 I could open a door that was facing my wheelchair
Q21 nquexped37 I was able to open the rings in school binders.
Q10 nquexped15 I was able to hold a plate full of food
Screw the cap off a bottle that has not been opened before
Q19 nquexped33 I was able to open a jar by myself.
Q3 posna_q8 Pour a half gallon of milk?
Q1 posna_q7 Lift heavy books?
Q20 nquexped36 I was able to pull open heavy doors.
Q13 nquexped17 I was able to pick up a gallon of milk with one hand and set it on the table

Conclusion

There is a clear need to look at person-reported outcomes of function relative to clinically derived milestones. They represent the same concept, and thus we expect them to be strongly related to one another – this is the point. One of the key challenges in drug development (32) as stated by the FDA is a lack of validated person-reported outcomes that can be used to demonstrate that 1) individuals in clinical trials can demonstrate "noticeable" differences in function, and 2) that by creating a set of questions relating to more community-based functions, we can tie observed differences or changes in clinically-measured function back to performance of those daily community-based functions. There are a host of therapeutic agents currently being tested in DMD. None of the drugs are expected to make major improvements in function, but may slow or stabilize progression of disease over short-term and potentially make improvements over the long-term.

A better understanding of community-based functions relative to clinically-measured outcomes places maintenance of stability of the disease in the context of activities of daily living that are important to the patients and their roles as active and participatory members of family, peer groups and society as a whole. This will lead to a better understanding of the natural history of Duchenne muscular dystrophy sources of variation between patients, and will improve our ability to predict the course of disease for groups of patients and individuals based on measurements at a given point in time. Doing so will improve our ability to predict and prepare families and patients for the necessary course of clinical care, and furthermore will help us to identify clinical trial cohorts in a much more refined manner.

As an initial step to developing and refining a formal tool, the construction of item lists representing multiple aspects of mobility using assessments from the UC Davis / CINRG Duchenne Natural History Study gives us insight into the utility of question items from multiple person-reported instruments. This will inform us during future efforts to develop compound clinical trial endpoints and computer adaptive testing (CAT)-based person-reported outcomes. Based on an overall construct of mobility using the WHO-ICF model, our list of items creates a continuous scale that spans ambulatory and non-ambulatory stages of the disease, which is critically needed for conduct of clinical trials. Overall model fit is good, and items sort in an order that is consistent with clinical progression of disease, with loss of endurance, followed by loss of mobility and ambulation, followed by loss of upper limb and finally hand function. Individual items show variation in overall model fit, and the final result still indicates a moderate degree of over-discrimination that suggests that there is still local dependency among items. This is not surprising given that the combined items were not formally developed as a unified scale, and given there is significant variability in both phenotype and rate of progression across the range of clinical function represented in this cohort. We see ceiling effects that suggest that inclusion of items representing higher levels of function might be necessary to assess less affected individuals. There is also a potential reduced sensitivity toward more severe end of the scale suggesting a need for inclusion of additional items at that end. However, the items adequately cover a population of children with early disease, adolescents who are transitioning between ambulatory and non-ambulatory phases of the disease (who are all currently being targeted for inclusion in clinical trials), and advanced-stage non-ambulatory individuals. Individual person fit indices for most of the cohort indicate a moderately good degree of model fit, and the Person Separation Index statistics indicate an moderately good ability to discriminate between individuals. While there is some local dependency of items, it is due in part to similarity of questions measuring the same types of tasks under the mobility construct. We reduced overall dependency somewhat by removing duplicative items where possible, and it is possible that this might be further reduced through construction of polytomous responses where multiple dichotomous questions currently exist. Overall, our data supports the concept that lists of commonly-themed items can be constructed from multiple concurrently administered instruments according to the latent domains they represent. In the mobility domain, we demonstrate that question items from existing PRO measures can be combined with clinically-derived functional "milestone" assessments on the same linearized scale, thus enabling measurements across multiple ages and stages of disease. Such lists should be refined into item banks with responses that can be used in development of targeted clinical trial assessments, PRO CAT tools, and potentially even self-reported measures of clinical function.

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PROTOCOL TITLE: Semi-structured interviews about a new a lifespan-based novel composite person-reported outcome instrument based on data from the CINRG Duchenne natural history study. (PI: E.K. Henricson)

1) Objectives

Specific Aim 1: We will conduct semi-structured interviews to identify cognitive understanding of person-reported outcome (PRO) questions and answers, and to adjust question wording and answer vocabulary as necessary.

Specific Aim 2: We will conduct semi-structured interviewsto identify relevant items for inclusion in a composite PRO measure, and to develop new items where suitable ones do not exist.

2) Background

Duchenne muscular dystrophy (DMD) is a disabling and life-threatening X-linked genetic disorder caused by defects in the gene for dystrophin, a protein that stabilizes muscle cell membranes [1]. It is the most common neuromuscular disease of childhood affecting 1 in 3,500-5,500 males with an estimated prevalence in the U.S. of 15,000 [2, 3]. Complete loss of dystrophin causes increased muscle fragility, and males with dystrophinopathy develop progressive loss of muscle fibers with replacement by fat and connective tissue, severe disabling weakness, contractures and scoliosis, loss of ambulation and self-care skills, respiratory and cardiac failure, and premature death [4, 5]. Becker muscular dystrophy (BMD), is a phenotypically milder form of dystrophinopathy due to in-frame mutations and partial loss of dystrophin and these patients exhibit later manifestation of symptoms [6]. DMD creates tremendous psychological and emotional burden as well as financial burden on patients, parents and caregivers, siblings, and other family and friends [7-12]. Patients with DMD also utilize considerable health, education, and community resources. DMD has been estimated to have the highest per capita costs for medical rehabilitation services of any childhood disability [13].

The past several years have seen a marked increased interest by pharmaceutical companies in conducting ground-breaking research and development into effective treatment agents for DMD. Therapeutic approaches under development for clinical trials in DMD include antisense oligonucleotide (AON) exon skipping therapies, gene therapy strategies, stem cell therapies, as well as a host of small-molecule therapies (e.g. compounds that induce read-through of premature stop-codon mutations, promotion of muscle growth via myostatin inhibition, utrophin upregulation, and steroid analogs with improved side effect profiles). While these therapeutic approaches will not be curative, there is significant hope that new therapies on the horizon will significantly alter disease progression, improve function, and improve quality of life. Ideal clinical endpoints used for future clinical trials need to be clinically meaningful both with regard to a) patient-reported outcome measures focused on well- being and health-related quality of life and b) clinically meaningful milestones such as loss of ambulation, self-feeding, and reliance on non-invasive ventilation. Currently, there is not a widely used patient reported outcome measure to accurately follow the progressive and predictable loss of muscle function in patients with Duchenne Muscular Dystrophy. Based on data from the CINRG Duchenne Natural History Study, a composite tool was created to specifically address this need. The Duchenne Muscular Dystrophy Lifetime Mobility Scale (DMD-LMS) is a patient / guardian-reported outcome instrument currently in development by UC Davis investigators that is focused on community ambulation and day to day mobility. The DMD-LMS is comprised of three subdomains representing 1) walking and moving, 2) transfers and trunk stability, and 3) carrying, moving and handling objects measuring from early ambulatory to late non-ambulatory stages of disease, and each subdomain is scored out of 100 points. The DMD-LMS, developed using Rasch analysis methods, has demonstrated internal validity and is capable of differentiating between steroid-treated and non-treated groups, between functional “milestone”

groups reflecting different degrees of disease progression, and has demonstrated significant change over one year across all stages of disease. ***A detailed technical report is available as an appendix to this application.***

There are two main recommendations resulting from the initial technical development phase of the instrument. The first recommendation was to standardize the presentation syntax and response options for questions throughout the study. We did this in order to mimic original questions whose response characteristics across multiple ages/stages of disease were stable and followed a logical order in correlation with progressive loss of function. The second recommendation was to create additional questions at the higher and lower ends of functional ability (ex. hopping and jumping vs. pushing buttons on a smart phone). We did this by reviewing commonly-used clinical functional evaluations and constructing analogous questions based on those functional tasks. Here, we are conducting this study to evaluate caregiver and patient perceptions of the final draft instrument to evaluate face validity and to confirm understanding of underlying concepts represented by each question, to evaluate questions as to their patient acceptance, and to identify alternative ceiling and floor items as identified by the participants themselves.

Participants:

Participants will include up to n=35 teens and adults with DMD, and n=40 parents/guardians of children and teens with DMD. Participants with DMD will be grouped into teens (n=20) and adult (n=15) categories. Parents/Guardians will be grouped into child (n=20) and teen (n=20) categories (see Table 1).

Table 1	**Parent/Guardian**		**Teen/Adult DMD**	
	Group A *Children with DMD Age 5-10*	**Group B** *Teens with DMD Ages 11-17*	**Group C** *Teens with DMD Ages 11-17*	**Group D** *Adults with DMD Age 18+*
1. Walking/Movement	5	5	5	0
2.Transitions	5	5	5	5
3.Upper Extremity 1	5	5	5	5
4. Upper Extremity 2	5	5	5	5
Total Surveys	**20**	**20**	**20**	**15**

Experimental Methods:

Using a collection of questions based on patient responses to established instruments, patient and parent focus group participants will complete a of the draft DMD-LMS composite measure during the course of routine clinical care and then participate in semi-structured interviews to validate this tool for broader use. A similar method was used to validate a short form version of a similar measurement for Myotonic Dystrophy, the MDHI [14]. Semi-structured interviews will be used to determine the comprehension, ease of use, response processes, and recall strategies (time frame of responses) of this instrument [15].

Speech-to-Text Data Capture

PROTOCOL TITLE: Semi-structured interviews about a new a lifespan-based novel composite person-reported outcome instrument based on data from the CINRG Duchenne natural history study. (PI: E.K. Henricson)

A majority of DMD patients in their late teens and onward experience limited hand mobility that precludes the use of a standard keyboard for data entry during questionnaire response. In addition, it is difficult for them to type longer qualitative responses such as the ones sought in this study. To this end, we are piloting the use of adaptive speech-to-text capabilities of the iPad to interface with REDCap to determine the feasibility of use in future questionnaire-based studies via the internet. Interviews will use the speech-to-text function of the Apple iPad to transcribe de-identified participant interviews. During interviews, participants will be asked to describe what each question means to them (comprehension probe), discuss how sure they were of their answers (confidence probe), discuss the perceived time frame of the responses, remark on the wording of each question and theme, comment on the response choices, report the time needed to complete the instrument, identify and problematic formatting issues, discuss the clarity of the instructions, comment on the scoring strategy, and identify any major mobility issues that were not addressed, including items that might lie outside of the current ceiling/floor thresholds of each of the 3 sub scales. Our study team will decide by consensus if specific questions should be reworded, removed, or replaced in order to create the final version of the DMD-LMS instrument.

The attached surveys will be administered using UC Davis REDCap with dedicated iPads that will be connected via WiFi. Patients of the UC Davis PM&R Pediatric Neuromuscular Clinic and Neuromuscular Research Center will be asked if they would like to participate in the study. If patients or guardians of patients wish to participate, they will be given a paper consent form by the study coordinator. Participants will be issued a subject ID that will consist of the group letter (A, B, C, or D), three-digit ID number (001, 002, etc.) and then the survey number (1, 2, 3, 4).

Coordinators will determine the appropriate survey based on the ambulatory status of the DMD patient as well as the previous surveys administered to the participant. The PRO survey will be broken up into four parts. Participants may elect to complete one or more surveys at one or more clinic or research appointments. After completing the consent form, the coordinator will instruct the participant on how to complete the online survey via REDCap. Participants will have approximately 15 minutes to complete 30 questions. Each question will ask about the DMD patient's ability to complete a specific task within the past 7 days. Participants will not have to have completed the listed task, but only reply based on the perceived ability to complete the listed task if necessary. After completing the survey, participants will be instructed to wait for study coordinator to return for an interview that will take approximately 15 minutes to complete. During this cognitive debrief section, patients will be asked about the appropriateness of each question they answered during the survey. Their answers will be repeated and they will be asked if they want to update their response. Participants will then be asked to comment if a question was offensive or if the wording of the question could be improved. This section will use the built in dictation function of the Apple iPad keyboard. The coordinator will ask the participant the question and then hit the microphone key on the iPad's keyboard to capture the participant's verbal response. The coordinator will then verify the speech-to-text dictation for inaccuracies or typos. If the participant is having difficulty speaking and recording their answers in this manner, then the coordinator will listen to the participant's response and then repeat it back to them so the speech-to-text function can capture the answer. The coordinator will note the cases in which they repeated participant's answers. If speech to text function is not working properly, then coordinator will type answers into REDCap text boxes. If the REDCap system is down, then the coordinator will use a printed copy of both the survey and interview to administer it to patients. This source document will be kept on file and the answers will be entered into the REDCap system.

3) Indicate the procedures that you will use to collect data.

☒ Surveys – Attach all surveys you will use in this study.

☒ Interviews – Attach an interview script with the questions that will be asked during the interview.

☐ Focus groups – Attach a summary of the questions and issues that will be discussed during the focus sessions.

☐ Observation of public behavior – Describe the behavior you will be observing below.

Click here to enter text.

☐ Other – Describe any other data collection or research procedures you will be conducting

Click here to enter text.

4) **Will you record any information that directly or indirectly identifies the individual on the data collection form (survey, interview responses or documentation of observations)?**

☐Yes

☒No

☐I am collecting data through more than one survey, interview or observation. Responses obtained from only the following will include direct or indirect identifiers:

Click here to enter text.

5) Participants' will be:

☐ Audiotaped
☐ Videotaped
Recordings will be labeled with direct or indirect identifiers: ☐ Yes ☒ No (Participants may use speech-to-text dictation system that is part of the iPad operating system that will not store audio files after processing).

6) Data Management and Confidentiality

Indicate how you will protect the data that you obtain and/or the information you record while conducting this study from disclosure to any individual who does not have a right or a need to access the information *(check all that apply)*

☐ Individual's responses/statements will not be linked to their identity. (No identifying information will be included on the documents/recordings and the documents/recordings will not be coded and linked to the individual's identity.)

☐ Individual's responses/statements will not include any information that identifies the individual, but the responses/statements will be coded and linked to their identity on a separate document or in a separate database.

☒ All identifiable electronic data will be maintained on an encrypted device requiring a password for access. Passwords will not be shared and will be protected from access.

☐ If the research includes review of medical or education records: Identifiable information from medical or education records will be stored on an encrypted device, investigators will follow applicable university policies (UC Davis Hospital Policy 1313, UCDHS P&P 2300-2499, and UC Business and Finance Bulletin on Information Security (IS-3).

☒ All paper records will be stored in a locked room/file-cabinet with access limited to only individuals who have a right and need for access.

☐ Other – (e.g. how will you manage the confidentiality for visual images and/or audio/video tapes?) Describe *Click here to enter text.*

7) Inclusion and Exclusion Criteria

Inclusion Criteria:

- Parent/Guardian Participants

  Participants must be the adult parent/guardian of a minor child from 5 to 17 years of age with a diagnosis of Duchenne muscular dystrophy, proven by either muscle biopsy or molecular diagnostics with a clinical picture consistent with a moderate to severe dystrophinopathy.

- Patients with DMD

  Participants must be at least 11 years of age and developmentally and cognitively capable of completing mobility questionnaires on a computer or tablet device.

- Proficiency in English
- Willingness to comply with study procedures

8) Study Timelines

The duration anticipated to enroll all study subjects for prospective data collection only:

☒ I will be enrolling subjects until: February 2017

The estimated date for the investigators to complete this study (complete primary analyses):

April 2017

9) Data Banking

Will data be banked for future use? ☒ Yes ☐ No

Note *- If data will be banked for future use, the aims of the study must justify the retention of the data and you will need to address the additional questions below and the consent form must indicate that data will be banked for future use.*

If yes, will the data that are banked be identifiable?

☐ Yes, the data will be identifiable

☒ No, the data will be completely anonymous.

☐ YES. No, the data will be stripped of identifiers and will be coded. The link to the individual's identity will not be made available to those requesting data from the data bank and will be maintained separately from the data bank.

Where will the data be stored?

UC Davis instance of REDcap

How long will the data be stored?

Indefinitely

Who will have access to the data?

Study team (PI, co-investigators)

Describe the procedures to release data, including: the process to request a release, approvals required for release and who can obtain data. Future studies using this data will have a separate IRB protocol and approval.

10) Risks to Subjects

☒ This data collection study poses the risk of loss of confidentiality. The risk will be minimized through the processes described above. This study will abide by all applicable law, regulations, and standard operating governing the protection of human subjects, student information and protected health information.

☐ Other – Describe: *Click here to enter text.*

11) Potential Benefits to Subjects

☒ The participants who complete surveys or participate in interviews, focus groups or observation of public behavior are not likely to receive any benefit from the proposed research but others may benefit from the knowledge obtained.

☐ Other – Describe: *Click here to enter text.*

12) Sharing of Results with Subjects

☐ Results will not be shared with subjects.

☒ Results will be shared with subjects – Describe: Results will be shared only in the form of a finalized survey which will undergo initial field testing through the Parent Project Muscular Dystrophy DuchenneConnect patient registry. That next phase of instrument development and testing will occur under a separate IRB approved study protocol that has yet to be developed.

Important note about consent for exempt research *- If this study meets the requirements for an exemption, you may use an abbreviated process for obtaining consent. Consent can be verbal, but you must provide the following information to participants through an information sheet or written script:*

- *The subject is being asked to participate in a research study;*
- *A description of the procedure(s) the participant will be asked to complete;*
- *Participation is voluntary; and*
- *The investigator's name and contact information.*

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